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NATIONAL RESEARCH COUNCIL

Manual of Clinical Mycology

Prepared Under the Auspices of the Division of Medical Sciences of the National Research Council

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INTRODUCTION

THIS VOLUME is one of a series developed under the auspices of the Division of Medical Sciences of the National Research Council to furnish the medical departments of the United States Army and Navy with compact presentations of necessary information in the field of military medicine.

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FOREWORDS

AT MOST of the medical schools in the United States there are few men who are capable of making gross identifications of the molds, yeasts, and yeast-like micro-organisms which are encountered in the lesions of patients, on their skin, or in exudates, sputum or other materials sent down to the laboratory "for diagnosis." There are even fewer in these schools who are capable of specific identification of the fungi—pathogenic or nonpathogenic. In medical and surgical clinics skin lesions caused by fungi are often discovered late after reference of the patient to a dermatologist. The lesions of the internal organs, lungs, liver or intestines are frequently diagnosed as mycotic only after long delays caused by prolonged "elimination" procedures, often impeded by a presumptive diagnosis of tuberculosis. In departments of pathology the discovery of fungi in tissues at autopsy, usually when stained sections are examined, causes a flurry of excitement; a search for pictures to match structures seen in the mounts; a vain attempt, after cultures are no longer possible, to establish an etiologic diagnosis on the basis of what the dead forms might have been; and the writing of additional incomplete and confusing papers. In many places in this country medical mycology is a field of esoteric interest.

It is to be regretted that practice is so far from reality. As a matter of fact, fungus infections are so prevalent that they should not be the field of interest of a few specialists, but deserve the attention of *all physicians*. As the authors of the *Manual* state in their preface, "Fungus infections are of such common occurrence that we have found it necessary to consider mycotic diseases in the differential diagnosis of practically every obscure infection." The same problems of differential diagnosis arise in many infections which are not so obscure.

Knowledge of fungus infections is of particular importance to medical officers in this war because thousands of men in the Armed Forces are engaged in the field in tropical regions in which mycotic infections are frequent. Medical officers caring for the health of these troops need to be provided with the latest and best information on the subject. Medical officers in this country under whose care returning soldiers will be placed need to have the same information readily available. Physicians under whose observation and care men of the service may come, through one or another arrangement, need to be familiar with mycologic technics and clinical differentials.

This *Manual of Clinical Mycology* performs services along all of these lines. It presents clearcut clinical descriptions. It clears up confusions in nomenclature and differential diagnosis of the mycotic diseases. It presents simplified and workable classifications and methods.

It is believed that this volume will be of general and practical value both to the mycologist and the clinician

NORMAN T. KIRK
Major General, U. S. Army
The Surgeon General.

PRIOR TO the onset of this great conflict, it would have seemed improbable, to say the least, that a Manual of Clinical Mycology would have been needed by the armed forces, that diseases of mycotic origin could become of such military significance as to require a volume such as this one.

The initial pressing problems of Burns, Shock, Wound Healing, of Abdominal and Genito-Urinary Injuries, of Plastic and Maxillo-Facial Surgery, of Neuro- and Thoracic Surgery, were of course those most urgent, most demanding analysis and coordination. The volumes on these aspects, sponsored then by the National Research Council, appeared promptly, were widely distributed and of great assistance, and have stood the test of these years

This new manual is just as much a military need Most textbooks on dermatology brush mycotic infections off too lightly, and the medical officer has fumbled with hoary formulas Our tropical warfare, particularly in the bush jungles of the South Pacific, has fostered fungus growth to a crippling degree.

The dermatomycoses, otomycosis, and maduromycosis, among the superficial types, coccidioidomycosis and blastomycosis among the infections with deeper manifestations, are discussed thoroughly and satisfactorily

The authors have not neglected either clinical or laboratory diagnosis. Treatment is definitive and modern. This volume is probably as highly to be commended both for soberness of presentation and for timeliness as any of its predecessors in this series

ROSS T. MCINTIRE
Vice Admiral, Medical Corps
Surgeon General, U S Navy

PREFACE

FUNGUS infections are of such common occurrence that we have found it necessary to consider mycotic disease in the differential diagnosis of practically every obscure infection. During the past ten years at Duke Hospital we have had the opportunity of studying all types of mycoses described in this manual. One of the greatest deterrents to the clinical study of fungus infections is the confusion concerning the mycologic nomenclature of the fungi pathogenic for man. Such confusion exists largely because the mycologic laboratory usually is too far separated from the clinic, and the personnel of most hospital laboratories is unacquainted with the methods of study used for identification of the pathogenic fungi.

It is obvious that knowledge concerning the clinical aspects of the mycoses can be obtained only when more cases are recognized and reported and that the diagnosis must be made by the clinical laboratory. For this reason, we have experimented with blood agar and incubated cultures at 37° C. in order to obtain characteristics which can be interpreted by the bacteriologist using media and technics to which he is accustomed.

A chapter has been included on the contaminants to which pathogenicity sometimes is erroneously attributed. There is another chapter on the fundamentals of mycology in which the descriptive terms used by mycologists are defined and illustrated. The classification of the pathogenic fungi has been simplified, in accord with the other investigators who are studying the mycoses. In some instances, the synonymies of the fungi have been abbreviated to conserve space. For example, only 11 of the 172 names for *Candida albicans* have been listed. To some, the classification presented in this manual may seem to be oversimplified, but, in our opinion, information concerning the mycoses is possible only if such a classification is employed—one which is sufficiently simplified to be used by the bacteriologist in a hospital laboratory.

In preparing this manual, each of the authors contributed a section for each chapter. The sections on symptomatology, differential diagnosis, prognosis and treatment of the systemic mycoses were prepared by David T. Smith, the mycologic sections by Norman F. Conant, the sections on pathology by Roger D. Baker, and those on geographic distribution and immunology by Donald S. Martin. The chapter on the clinical aspects of the dermatomycoses was written by

Jasper L. Callaway, as were the clinical descriptions of the other superficial mycoses. In order to coordinate the various sections and to make the style more uniform, the manuscript was rewritten by Donald S. Martin.

We are indebted to Dr. Frederic M. Hanes who read the entire manuscript and made many valuable suggestions.

We are indebted to Robert E. Little, Carl M. Bishop, Elon H. Clark and Carlin P. Graham for the making of many of the photographs and illustrations. We would like to express appreciation to Mrs. Doris Coltrane Grimes and Mrs. Helen Shipp Johns for their valuable technical assistance and to acknowledge the extremely valuable assistance of Mrs. Eugenia Speed Pulliam who cheerfully has typed and retyped the manuscript many times.

Particularly, we wish to thank the John and Mary R. Markle Foundation, whose grants made possible many of the fundamental studies out of which this manual was developed.

THE AUTHORS.

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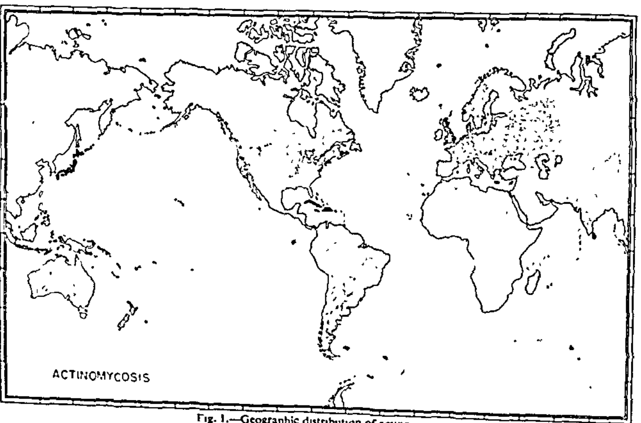


Fig. 1.—Geographic distribution of actinomycosis.

Chapter I

ACTINOMYCOSIS

(*Lumpy Jaw, Streptothricosis, Nocardiosis*)

THIS INFECTION, the commonest of the systemic mycoses, is caused by a group of fungi more closely related to bacteria than are any of the other fungi. Reproducing by simple branching only, the filaments are approximately the same width as tubercle bacilli, and in culture the fungus produces colonies not unlike certain bacteria.

Definition.—Actinomycosis, caused by *Actinomyces bovis* or several species of the genus *Nocardia*, is a chronic disease characterized by the formation of granulomatous lesions which tend to break down, form abscesses and discharge through multiple draining sinuses In the lesions, sinus walls or discharges are found either the characteristic "sulfur granules" or small, tangled masses of gram-positive branching filaments which may or may not be acid-fast.

Geographic Distribution.—The world-wide occurrence of actinomycosis is illustrated best by Cope's statement that ". . . wherever there is a microscope and a laboratory, the fungus has been found to be the cause of disease." (Fig. 1.)

Source of Infection.—The aerobic actinomycetes of the genus *Nocardia* have been isolated from the soil, but the anaerobic *Actinomyces bovis* has not been found in vegetative material Lord and Trevitt, Naeslund, Emmons, Slack and others have demonstrated the presence of pathogenic *A. bovis* in the tonsils and around the carious teeth of apparently normal individuals, indicating that the source of infection in most cases of actinomycosis probably is endogenous

Age, Sex, and Occupation Incidence.—Actinomycosis has been observed in a 28-day-old infant and in a patient 75 years of age The disease is rare in children under 10 years of age, the majority of the cases occurring between the ages of 15 and 35 Infection occurs in



Fig 2 —Actinomycosis of the face Note swelling of subcutaneous tissues and multiple sinus formation

approximately twice as many males as females. It is stated frequently that agricultural workers are infected more often than those engaged in other occupations, which suggests that the infection is acquired from some exogenous source; however, in view of our present knowledge concerning the presence of *Actinomyces bovis* in the mouth, the higher incidence in this class of workers may be due to poor oral hygiene.

SYMPTOMATOLOGY

The clinical picture varies with the location of the disease, as does the prognosis Cope's series of 1330 cases, collected from the literature, revealed that 56 8 per cent began in the neck, 22.3 per cent in the abdomen, 15 per cent in the thorax and 5 9 per cent in other parts of the body. The tongue was infected in 3 per cent. In rare instances, isolated lesions have been described in the skin, kidneys, genital tract, liver, ovaries, bones, joints and central nervous system; these structures frequently are involved when a primary lesion in the neck, thorax or abdomen develops into a generalized infection.

It is customary to classify the disease clinically into cervicofacial, thoracic and abdominal actinomycosis, depending upon the site of the initial infection.

Cervicofacial Actinomycosis.—Cervicofacial actinomycosis is the commonest form of the disease and, fortunately, has the best prognosis The organisms enter presumably through the mucous membranes of the mouth and pharynx, by way of the gums about carious teeth or through the tonsils Occasionally, the salivary and lacrimal glands are invaded by direct extension through their ducts. The orbit may be involved by extension of the infection from the sinuses More rarely, the infection begins lower in the pharynx, producing a peri- [illegible]

Most frequently, the infection is noted first in the lower jaw, particularly in the region of an infected tooth or in the socket left by a recent extraction. A history of previous toothache or other dental affection frequently is obtained The swelling usually is most marked over the angle of the mandible, but may be posterior to it if the fungus gained entrance through the tonsils

The swelling in the soft tissues of the face is not characteristic at first, but the overlying skin soon assumes a dark red or purplish color, the tumor develops a "wooden" type of hardness and the

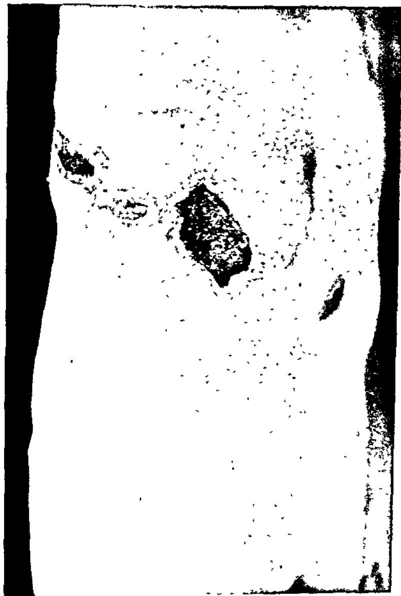


Fig. 3.—Actinomycosis of the thorax with multiple sinuses in the skin.

surface appears uneven or "lumpy." As the disease progresses, abscesses develop and multiple sinuses appear. (Fig. 2.) Trismus is a frequent symptom when the muscles of mastication are affected. Pain is minimal unless there is a marked secondary infection, and the general health of the patient remains good if the disease remains localized to the face and neck areas.

X-RAYS.—Roentgenograms of the bones show no involvement of bone in the early stages of the disease, but later there may develop periostitis, true osteomyelitis with bone destruction or central rarefying osteomyelitis expanding the cortex into a pseudocyst.

Thoracic Actinomycosis.—Primary infection of the lung with *A. bovis* results probably from aspiration of infected material from the mouth. The aerobic actinomycete (*Nocardia*) may be inhaled with dust, straw or other extraneous material.

The SYMPTOMS in the first few weeks of the disease are those of a subacute pulmonary infection with a mild, irregular fever, cough and some expectoration. As the disease progresses and small abscesses develop in the lungs, the sputum becomes mucopurulent and may contain blood Involvement of the pleura may cause pleural pain. Although some patients develop pleural effusion, the fungus more often invades directly through the chest wall, producing numerous draining sinuses (Fig 3.) The patient loses weight and strength, becomes anemic, and may develop spiking temperature, night sweats and dyspnea or other signs of severe pulmonary disease Dysphagia can result from mediastinal invasion, and the infection may extend to the pericardium and heart.

The PHYSICAL SIGNS in the early stages resemble those of tuberculosis except that the primary sites of infection in pulmonary actinomycosis are found most frequently at the lung bases. Massive areas of dulness develop later; the chest wall may be retracted and limited in motion The heart may be displaced The presence of subcutaneous abscesses or open, draining sinuses should suggest the diagnosis.

X-RAYS—Chest films show smooth, massive areas of consolidation, often containing several small, ill-defined areas of rarefaction The lesions are usually bilateral and occur most often in the lower half of the lungs, but they may be limited to a single upper lobe (Fig. 4) Areas of massive consolidation may project from the hilum, suggesting neoplasm The pleura is involved in most of the advanced cases, either as massive pleural adhesions or as accumulations of fluid which may or may not be encapsulated The ribs are



Fig 4.—Actinomycosis involving the right upper lobe. The etiologic agent was the acid-fast *Nocardia asteroides* Cured with sulfadiazine and potassium iodide



Fig 5 —Actinomycosis of the spine There is a hyperplastic reaction in the spinous processes and in the cortex on the right side The bodies of the vertebra are not infected.

invaded frequently and show both destructive and proliferative changes.

Abdominal Actinomycosis.—The organisms, which enter through the mucosa of the intestinal tract, probably represent oral strains of *Actinomyces* which have been swallowed with the saliva. The infection may reach the abdomen by metastasis or direct extension from the thorax, but more often the reverse process is observed, the infection extending from the abdomen to the chest.

The first SYMPTOMS are found usually in the ileocecal region, presenting a picture suggesting acute or subacute appendicitis. These *symptoms are often minimal, the first indication of infection being* the development of an indistinct, irregular mass in the ileocecal region or elsewhere in the abdomen. Infection beginning in the transverse or descending colon simulates carcinoma. As the disease [illegible]

pyelonephritis. The infection may spread to the vertebral bodies, leading to compression of the spinal cord or the formation of a psoas abscess.

The most common PHYSICAL FINDINGS are those of a tender, palpable mass in the region of the appendix although masses may be found in any part of the abdomen. Actinomycosis rarely is diagnosed before exploratory laparotomy unless draining sinuses are present in the abdominal wall The liver and spleen may be enlarged

X-RAYS.—Roentgenograms of the abdomen may show masses, enlargement of liver or spleen or involvement of the vertebral bodies. Simpson and McIntosh emphasize that the changes of periostitis with erosion of the cortical portion of the bone and destruction of the laminae, articular facets, transverse and spinous processes suggest [illegible]

Laboratory Examination.—Except for the demonstration of the organisms by direct examination or culture, laboratory procedures are of little value. In progressive actinomycosis, the *sedimentation* rate is elevated, there is usually a leukocytosis and a relative increase in the neutrophils.



Fig 6.—*Actinomyces bovis* Sterile saline compress removed from patient with abdominal actinomycosis after twelve hours Granules caught in webs of gauze

MYCOLOGY

The fungi causing actinomycosis belong to two well-defined biologic types, namely, anaerobic and aerobic. The *anaerobic* type consists of a single species, *Actinomyces bovis*, which is gram-positive and non-acid-fast. The *aerobic* type includes several species, all of which are gram-positive with some species being acid-fast. Of the acid-fast group, *Nocardia asteroides* and *N. gypsoides* have been studied the most extensively. It is thought that many of the described species (including *N. gypsoides*) placed in this aerobic group are variations of *N. asteroides* and should be reduced to synonymy with it, simplifying the taxonomy of the group The aerobic non-acid-fast group includes *N. madurae* and several others which are doubtfully valid species.

Species in the aerobic group have been separated on such biologic activities as ability to produce disease in experimental animals, to liquefy gelatin, to peptonize milk or to give a tyrosinase reaction. It is agreed, however, that these characteristics do not remain constant, and it seems more valuable to classify these fungi by their acid-fast properties. Slight differences in the shade or intensity of pigmentation, ability to liquefy gelatine or to peptonize milk, and so on, should be evaluated critically for the purpose of reducing rather than enlarging the number of species

Direct Examination.—Pus may be collected from the draining sinuses by holding a sterile test tube at the edge of the lesion, allowing the pus to run down the sides of the tube, such tubes should be held to the light and examined for the presence of small granules. If granules are not seen in freely flowing pus from sinuses, the walls should be curetted and the material examined Failure to find granules may be overcome occasionally by applying dry, sterile gauze pads to the sinuses, where they are allowed to remain in position overnight; the next morning granules may be seen on the gauze dressing (Fig 6) Sputum should be spread in a sterile petri dish and examined carefully for granules.

The granules are examined microscopically as fresh preparations by placing a loopful of the infected material containing a granule on a slide and gently crushing it under a cover glass. These granules appear as lobulated bodies composed of delicate branching, intertwined filaments (1 μ in diameter), the ends of which frequently are surrounded by a gelatinous sheath, giving a club-shaped appearance to the ends of the filaments These club-shaped structures are seen in optical sections around the periphery, giving the picture of a

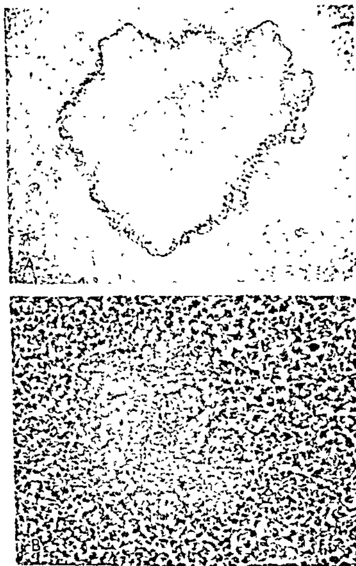


Fig 7 —*Actinomyces bovis* *A* Granule with clubs, in pus. × 450 *B* Granule without clubs, in pus × 450

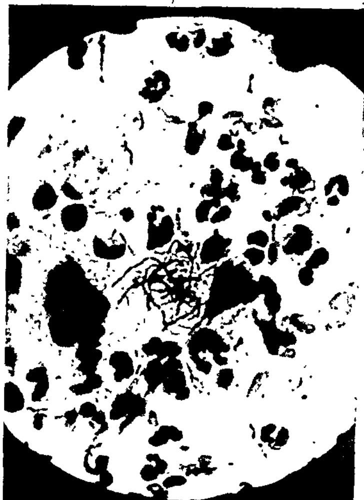


Fig. 8.—*Actinomyces bovis* Branching gram-positive filaments seen when granule is crushed and stained by Gram's method. × 1300

typical granule with clubs, hence, the name "ray fungus." (Fig. 7 *A*.) The diagnostic significance of these clubs has been overestimated since granules without them (Fig. 7 *B*) may be found along with clubbed granules in material from the same source. All granules should be crushed and stained by Gram's method to demonstrate the presence of gram-positive branching elements. (Fig. 8.)

Organized granules may not be present in spinal fluid or sputum, hence stained smears should be examined for the presence of short branching gram-positive or acid-fast elements

Cultures.—If the culture is to be made from pus, spinal fluid or material in which bacterial or mycotic contaminants are unlikely, the material should be inoculated into a deep tube of beef or veal infusion broth (*p*H 7.6–7.8) and streaked heavily on the surface of several Sabouraud's glucose agar slants If the material to be cultured is sputum, drainage from sinus walls or scrapings, it should be inoculated into veal infusion glucose agar shake tubes and streaked on the surface of Sabouraud's glucose agar slants. Beef infusion glucose agar or Douglas's agar shake tubes may be substituted for the veal infusion glucose agar media

A bovis grows in the bottom of the broth tubes as small, "fuzzy," white colonies which are easily broken up by shaking. In the shake tubes the fungus appears in 3 to 4 days as small, white, "fuzzy" or lobulated colonies 5 to 10 mm below the surface of the agar Larger colonies may be distributed throughout the depths of the culture (Fig. 9 *A*)

[illegible] positive, and small fragments frequently give the appearance of diphtheroids

Nocardia asteroides appears on the surface of Sabouraud's glucose agar slants incubated at room temperature or 37° C The colonies are glabrous, irregularly folded and vary in color from pale yellow to deep orange (Fig 10) *N. gypsoides* is said to differ by the chalky [illegible] The aerobic species *N. madurae* develops as a glabrous, waxy, wrinkled, cream-colored colony, later becoming

pinkish to varying shades of red. Microscopically, it resembles other species of *Nocardia* except that it is not acid-fast.

Animal Inoculation.—Sputum can be inoculated subcutaneously into guinea pigs if acid-fast *Nocardia* is suspected. The fungus, however, does not survive the treatment used in concentrating sputum for tubercle bacilli. The pathogenicity of pure cultures can be proved by intraperitoneal inoculation of guinea pigs.

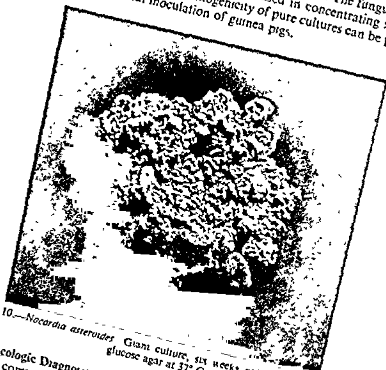


Fig. 10.—*Nocardia asteroides*. Giant culture, six weeks old, on Sabouraud's glucose agar at 37° C.

Mycologic Diagnosis.—All granules should be crushed and proved to be composed of gram-positive branching elements of bacterial width (1 μ) to distinguish actinomycosis from botryomycosis. Acid-fast branching forms seen in sputum should be differentiated from tubercle bacilli by culture and guinea pig inoculation. Infection with *Nocardia* will not occur in pigs receiving material concentrated by the methods used to concentrate tubercle bacilli.

While granules containing gram-positive branching elements are diagnostic, cultures should be made and identified.

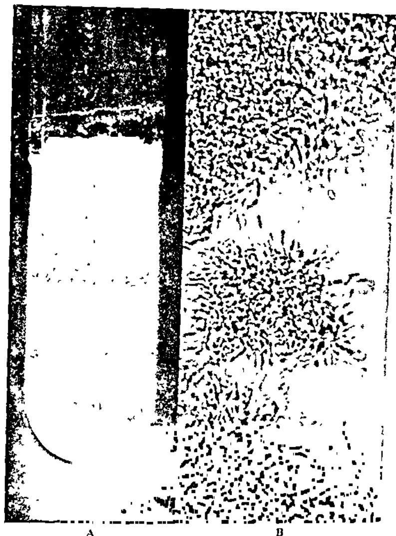


Fig 9 – *Actinomyces bovis* A Deep beef infusion glucose agar (pH 7 6) shake culture showing band of growth 1 cm from surface B Crushed colony from deep shake culture 850

pinkish to varying shades of red. Microscopically, it resembles other species of *Nocardia* except that it is not acid-fast.

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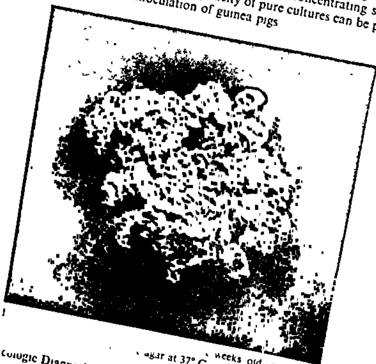


Fig. 1 … weeks old, on Sabouraud's agar at 37° C …

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Actinomyces bovis Harz, 1877. Synonymy.—*Discomyces bovis* Rivolta, 1878; *Nocardia actinomyces* Trevisan, 1889; *Cladothrix bovis* Macé, 1891; *Streptothrix actinomyces* Rossi-Doria, 1892; *Actinomyces Israeli* Dodge, 1935.

Nocardia asteroides (Eppinger) Blanchard, 1896. Synonymy.—*Cladothrix asteroides* Eppinger, 1890; *Streptothrix asteroides* Gasperini, 1891; *Actinomyces asteroides* Gasperini, 1894; *Actinomyces gypsoides* Henrici and Gardner, 1921.

Nocardia madurae (Vincent) Blanchard, 1896. Synonymy.—*Streptothrix madurae* Vincent, 1894; *Oospora madurae* Lehmann and Neumann, 1896; *Actinomyces madurae* Lachner-Sandoval, 1898; *Discomyces madurae* Gedoelst, 1902; *Nocardia indica* Chalmers and Christopherson, 1916.

PATHOLOGY

Suppuration, sinus and scar formation are characteristic of actinomycosis. Burrowing of the abscesses occurs frequently, and the process may be active at one site and healed at another. The reacting cells immediately around the actinomycotic granules are usually polymorphonuclear neutrophils, but giant cells are occasionally in contact with the sulfur granule. (Fig. 11.) Macrophages may be present in large numbers at the periphery of the abscess and may contain sufficient fat to give a yellow color to the lesion which is visible to the naked eye.

Biopsy.—Tissue removed surgically usually is taken from sinuses but may come from bone, tongue, lymph nodes or isolated lesions.

The HISTOLOGIC APPEARANCES in these various sites are similar. The reaction may be that of a purulent infection with polymorphonuclear cells, or it may show nothing but the cells of chronic inflammation In other stages, granulation tissue or dense scar formation may be found. A biopsy from an abscess wall or sinus may not contain granules, the section showing only chronic inflammation. In such cases pus should be examined carefully. In some instances, the repair process has gone so far that only dense scar tissue can be seen.

The diagnosis is established histologically only by finding of the actinomycotic granule, although the presence of separate mycelial segments suggests the diagnosis These granules vary in size from those visible to the naked eye to those composed of only a few filaments, and are best located in histologic sections by searching for them within minute abscesses

In sections stained with hematoxylin and eosin, the central portion of the granule tends to stain more heavily with hematoxylin, the periphery better with eosin; but variations in staining occur, depending upon fixation. Peripheral eosin-staining "clubs" may or may not be prominent. (*Fig. 12.*)

When granules are found in sections stained with hematoxylin and eosin, it is important to stain by Gram's method. This shows the branching mycelium to be gram-positive, a valuable differential point in excluding other forms of granules. (Fig. 13.) In infections caused by *Monosporium apiospermum* (see MADUROMYCOSIS), spore forms can be identified near the periphery of the granule. If a granule is found as a result of bacterial infection, the organisms, which are usually gram-positive staphylococci, can be differentiated easily. These bacterial infections often are associated with foreign bodies and may simulate actinomycosis closely, accounting for the use of *the terms "botryomycosis" or "staphylococcic actinophytosis" for* a non-mycotic disease. It is desirable, also, to stain the organism in section to determine if it is acid-fast.

In biopsy material, actinomycosis may be confused with tumor or with chronic suppurative processes due to other causes Tissue from lesions of the neck, for example, may resemble sarcoma. Lesions of the breast may simulate either tumor of the breast or abscesses due to bacterial infection.

Autopsy.—Occasionally, the diagnosis of actinomycosis is not established until the autopsy is performed. The appearances at autopsy will depend largely upon the portal of entrance of the fungus Actinomycosis of the NECK and FACE, the commonest form of actinomycosis, is rarely encountered at autopsy, but death may result from extension of the process from the angle of the jaw upward along the cervical spine and into the cranial cavity or downward to the superior portion *of the thoracic cage Extensive osteomyelitis of the spine and of the* skull may occur. In such a case, recently observed, an epidural abscess with great thickening of the skull was found. The involvement of the orbital cavity on one side was so extensive that unilateral exophthalmus was produced

When the infection begins in the LARGE INTESTINE OR APPENDIX, minute abscesses of the mucosa or submucosa or sometimes large ulcers may be found Ramifying abscesses of the right lower quadrant or some other portion of the abdominal cavity may be encountered Rather characteristic is extension from the retrocecal region along



Fig. 13 — Edge of actinomycotic granule stained by Gram's method (MacCallum's stain) to show mycelium × 1500

the iliopsoas muscle, or around a kidney, with sinuses draining to the skin in the inguinal region or flank.

Extension to the LIVER by the portal vein is common, at times with an actinomycotic pylephlebitis and multilocular abscesses in the liver. The hepatic lesions often show much gray scar tissue and yellow-appearing areas. Extension from the liver to the subdiaphragmatic region, pleural cavity and lung is not unusual. Extension by the hematogenous route from the intestine may cause infection of the lungs, brain, meninges or other tissues without evidence of hepatic actinomycosis, but this is unusual.

Primary actinomycosis of the LUNGS may result in the formation of chronic abscesses, bronchiectasis or dense fibrosis. Extension to the pleura and chest wall or to the pericardium and heart may occur.

IMMUNOLOGY

Serology.—Although opsonins, agglutinins, precipitins and complement fixing antibodies have been reported to occur in the sera of patients with actinomycosis, the results have not been sufficiently clear-cut to warrant the use of serologic methods as a diagnostic procedure. There are certain technical difficulties in the preparation of smooth homogenous antigen suspensions, and in many instances investigators have reported cross-reactions with unrelated fungus antigens.

Hypersensitivity.—That patients with actinomycosis become sensitized to the fungus has been established. Intracutaneous injections into patients of vaccines or culture filtrates have resulted in local reactions with pain, redness and edema. Subcutaneous injections have caused local and focal reactions, as well as generalized symptoms and fever.

Drake and Henrici were able to produce specific hypersensitivity in guinea pigs and rabbits by the intratesticular injection of oily suspensions of the acid-fast *N. asteroides*. Intracutaneous injection of heat-killed vaccines produced no reactions in these animals, but injection of suspensions of living *Nocardia* produced non-specific toxic reactions in the infected and control animals. However, the injection of a crude extract prepared from powdered organisms, rendered lipoid-free by acetone extraction, resulted in a specific allergic reaction of the tuberculin type. The same type of response was elicited by injection of a protein fraction, the polysaccharide fraction produced a maximal reaction in 24 hours which disappeared

after 4 days. Although patients have not been tested with the antigens derived from cultures of *Nocardia*, the results obtained with them in experimental animals parallel closely the reactions obtained by injecting extracts of *Blastomyces dermatitidis* into patients with blastomycosis. It is not unreasonable to assume that non-toxic extracts of *Nocardia* will prove to be of value as diagnostic skin testing materials, and the possibility that these antigens could be used as desensitizing agents in hypersensitive patients should be investigated.

DIFFERENTIAL DIAGNOSIS

Actinomycosis presents such a variety of clinical pictures that it *must be differentiated from tuberculosis, syphilis, neoplasm, glanders*, tularemia, granuloma inguinale, osteomyelitis, staphylococcic actino- [illegible] nic appendicitis, ame- [illegible] tines, intestinal tuber- [illegible] of the retroperitoneal tissue or iliac bones and certain other types of mycoses, especially North American and South American blastomycosis, coccidioidomycosis, cryptococcosis and sporotrichosis

PROGNOSIS

The prognosis is best in the localized dermal and cervicofacial types, it is grave in all other types of infection, particularly in the abdominal form.

TREATMENT

The general resistance of the patient should be supported by rest in bed and a good diet supplemented by vitamins, especially cod liver oil and fruit juices.

Surgical Treatment.—Adequate SURGICAL DRAINAGE is essential, and since the sulfonamides protect against many of the dangerous secondary infections, the surgeo [illegible] ord to be radica [illegible] inus tracts should be explored and [illegible] d as much of [illegible] ly damaged tissues excised as is [illegible] esection of [illegible] testines is justifiable. Pleural [illegible] surgical [illegible] pulmonary lesions usually dra [illegible] e bronchi [illegible] or pneum [illegible] robably [illegible] n selected [illegible] have faile [illegible] to other [illegible] y.

Medica [illegible] The su [illegible] reason [illegible] in the t [illegible] *A. bo* [illegible] infect [illegible]

commonly used sulfonamides seem to affect the fungus. Sulfadiazine seems to be the drug of choice at the present time although the newer sulfamerazine has the theoretical advantages of slower absorption and excretion and is less likely to precipitate out in the urine. The best results have been obtained when sulfonamides, surgery and iodide therapy have been combined.

As soon as the diagnosis is established, treatment with one of the sulfonamides should be started and surgical drainage carried out while the patient has a sulfonamide level in the blood of 4 to 6 mg. per cent. After the acute effects of the operation are over, POTASSIUM IODIDE in saturated solution is started at the usual dose of 3 drops [illegible]

[illegible]

months. After the patient is "apparently well," the sulfonamides and iodides may be discontinued; they should be started again if symptoms recur. New foci, if present, should be treated surgically.

SODIUM IODIDE has been administered intravenously in daily doses of 1 Gm. as a substitute for the oral potassium iodide treatment THYMOL in daily oral doses of 1 Gm. or three doses of 0.5 Gm. has been used with success in some cases. In our experience, it has no advantage over the iodides and is much less effective than the sulfonamides

VACCINE THERAPY has been used with some success as a supplement to adequate surgical drainage. Colebrook, using stock and autogenous vaccines, treated twenty-three patients, using a dose of 5 to 10 million mycelial fragments at intervals of five days. Vaccine therapy may be tried if the patient fails to respond to surgery, sulfonamides and iodides'

The use of X-RAYS and RADIUM is advantageous in the treatment of certain cases, especially when indolent internal or external lesions are present.

There are a few reports which suggest that PENICILLIN is effective in actinomycosis Definite evidence of clinical improvement may appear in two to four days after the beginning of penicillin therapy, and the improvement is much more rapid than with the sulfonamides [illegible]

[illegible]

been reported as giving excellent results

after 4 days. Although patients have not been tested with the antigens derived from cultures of *Nocardia*, the results obtained with them in experimental animals parallel closely the reactions obtained by injecting extracts of *Blastomyces dermatitidis* into patients with blastomycosis. It is not unreasonable to assume that non-toxic extracts of *Nocardia* will prove to be of value as diagnostic skin testing materials, and the possibility that these antigens could be used as desensitizing agents in hypersensitive patients should be investigated.

DIFFERENTIAL DIAGNOSIS

Actinomycosis presents such a variety of clinical pictures that it must be differentiated from [illegible] biasis, typhoid fever, carcinoma of the intestines, intestinal tuberculosis, liver abscess, psoas abscess, sarcoma of the retroperitoneal tissue or iliac bones and certain other types of mycoses, especially North American and South American blastomycosis, coccidioidomycosis, cryptococcosis and sporotrichosis.

PROGNOSIS

The prognosis is best in the localized dermal and cervicofacial types, it is grave in all other types of infection, particularly in the abdominal form

TREATMENT

The general resistance of the patient should be supported by rest in bed and a good diet supplemented by vitamins, especially cod liver oil and fruit juices.

Surgical Treatment.—Adequate SURGICAL DRAINAGE is essential; and since the sulfonamides protect against many of the dangerous secondary infections, the surgeon can afford to be radical All sinus tracts should be explored and drained, and as much of the severely damaged tissues excised as is practical. Resection of loops of intestines is justifiable. Pleural lesions require surgical drainage, but pulmonary lesions usually drain through the bronchi Lobectomy or pneumonectomy probably will be used in selected cases which have failed to respond to other types of therapy.

Medical Treatment.—The SULFONAMIDES are reasonably effective in the treatment of both *A bovis* and *Nocardia* infections. All the

[illegible]

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Chapter II

NORTH AMERICAN BLASTOMYCOSIS

(Gilchrist's Disease)

ALTHOUGH the organism causing this infection appears in the tissues as a round, budding, yeastlike fungus (or "blastomycete"), it produces aerial hyphae on Sabouraud's medium incubated at room temperature. This distinguishes the infection from cryptococcosis or "European blastomycosis" which retains its yeastlike characteristics in cultures.

Definition.—North American blastomycosis is a chronic infection, caused by *Blastomyces dermatitidis*, characterized by the formation [illegible]

England, the remaining cases all have been found within the borders of the United States. (Fig. 14.) The mycologic findings in cases reported from other parts of the world have been described so inadequately that they cannot be accepted as examples of blastomycosis of the Gilchrist type.

Source of Infection.—Man presumably derives his infection from some exogenous source. The disease is not contagious, but in a few instances the infection has been acquired by direct inoculation or prolonged physical contact with an infected individual. A physician infected himself while performing an autopsy, and the infection has been transmitted to the back of an infant from a cutaneous lesion on the arm of a nurse.

NOCARDIOSIS

Actinomycosis caused by certain strains of aerobic actinomycetes, now called *Nocardia*, presents a clinical picture indistinguishable from the disease caused by *A. bovis*. The disease begins most often in the thorax, but usually spreads to other parts of the body. Some of the aerobic forms are partially acid-fast, but all are gram-positive and branching forms occur both in the tissues and in cultures.

MADUROMYCOSIS

Infections of the skin, subcutaneous tissues and bones of the extremities may be caused by either *A. bovis* or one of the aerobic actinomycetes (*Nocardia*) with the production of the clinical picture of Madura foot or mycetoma. This type of infection will be discussed in the chapter on maduromycosis. (p. 179)

ERYTHRASMA

In scrapings of superficial skin lesions, numerous narrow branching filaments resembling actinomycetes may be seen. These organisms, which have been cultured only rarely, have been described as *N. minutissima*. Since this fungus is found only in the superficial skin, it will be discussed in a separate chapter (p 282).

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Chapter II

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(*Gilchrist's Disease*)

ALTHOUGH the organism causing this infection appears in the tissues as a round, budding, yeastlike fungus (or "blastomycete"), it produces aerial hyphae on Sabouraud's medium incubated at room temperature. This distinguishes the infection from cryptococcosis or "European blastomycosis" which retains its yeastlike characteristics in cultures

Definition.—North American blastomycosis is a chronic infection, caused by *Blastomyces dermatitidis*, characterized by the formation of suppurative and granulomatous lesions in any part of the body but with a predilection for the skin, lungs and bones

Geographic Distribution.—Except for several proved and presumptive cases of *B. dermatitidis* infection reported from Canada and England, the remaining cases all have been found within the borders of the United States (Fig 14.) The mycologic findings in cases reported from other parts of the world have been described so inadequately that they cannot be accepted as examples of blastomycosis of the Gilchrist type.

Source of Infection.—Man presumably derives his infection from some exogenous source The disease is not contagious, but in a few instances the infection has been acquired by direct inoculation or prolonged physical contact with an infected individual A physician infected himself while performing an autopsy, and the infection has been transmitted to the back of an infant from a cutaneous lesion on the arm of a nurse.

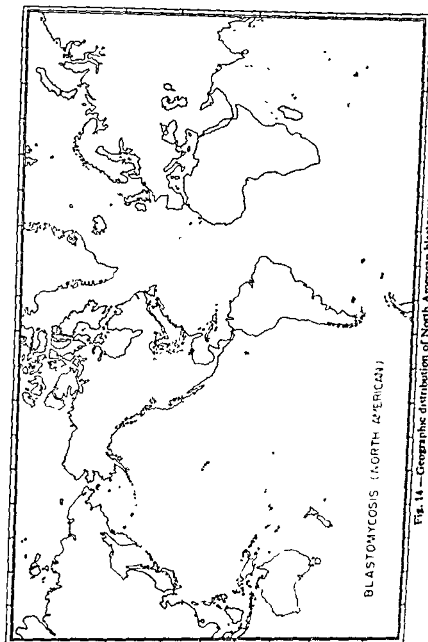


Fig. 14.—Geographic distribution of North American blastomycosis

Two cases of natural infection in dogs have been reported. The morphologic characteristics of the fungus in the tissues and in culture were identical with those seen in human infections. The serum from one of these dogs fixed complement with antigens prepared from human strains.

Age, Sex, and Race Incidence.—The disease has been described in patients as young as 6 months and as old as 80 years. In the series of 347 cases collected by Martin and Smith, more than 50 per cent were between the ages of 20 and 40, and the ratio of males to females was approximately 9 to 1. All races appear to be equally susceptible and the disease is more common among the poorer classes.

SYMPTOMATOLOGY

Two clinical types of the infection are recognized: systemic or disseminated blastomycosis and cutaneous blastomycosis. Although both clinical forms are caused by the same fungus, the cutaneous infection rarely spreads to involve organs other than the skin and subcutaneous tissues.

Systemic Blastomycosis.—The portal of entry in systemic blastomycosis usually is the respiratory tract. In an analysis of cases studied at necropsy, 95 per cent were shown to have pulmonary infection, and in more than half the cases the lungs showed the most extensive lesions. Dissemination throughout the body occurs as the disease progresses, resulting in lesions most commonly in the skin, subcutaneous tissues and bones. Bone infection is found in approximately 60 per cent of cases, the vertebrae and ribs being involved most frequently. Invasion of other organs occurs also, an analysis [illegible]

are small and unimportant. Infection of the intestinal tract is unusual, a valuable point in differentiating this disease from histoplasmosis and South American blastomycosis.

CLINICAL COURSE.—The onset often is insidious, and the infection may be widespread before the correct diagnosis is suspected. The illness usually begins as an ordinary subacute respiratory infection with dry, hacking cough, pain in the chest, low grade fever and some dyspnea. After a period of weeks or months, the sputum becomes purulent and may be blood streaked. As the pulmonary infection progresses, the dyspnea increases, the fever is higher, there is marked

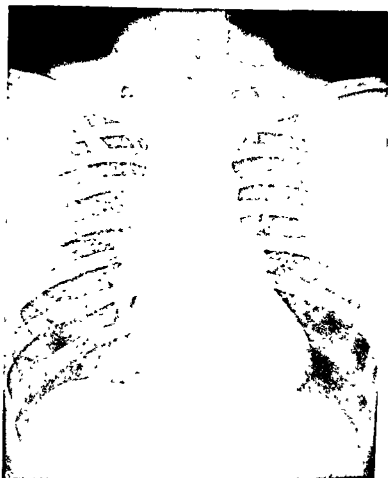


Fig 15 —North American blastomycosis The disease apparently is confined to the hilar and mediastinal lymph nodes



Fig 16 —North American blastomycosis of the lungs. Note the wedge-shaped shadow projecting into the right lung field.

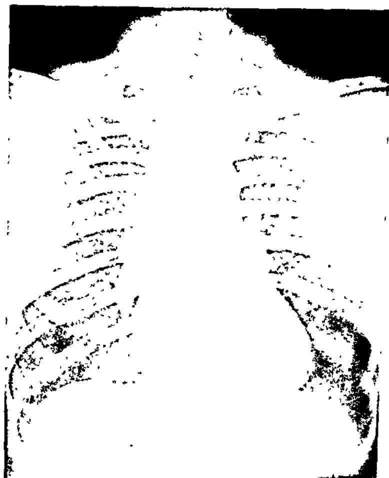


Fig 15 —North American blastomycosis The disease apparently is confined to the hilar and mediastinal lymph nodes

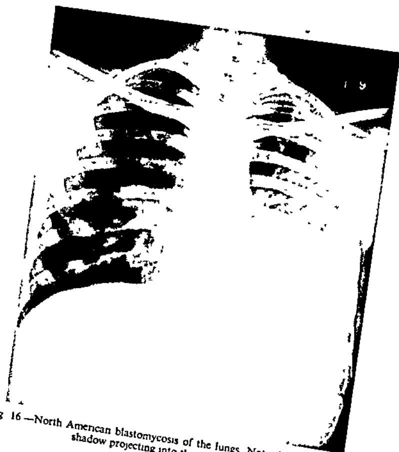


Fig 16 —North American blastomycosis of the lungs Note the wedge-shaped shadow projecting into the right lung field

loss of weight and strength and the patient develops night sweats. The sputum increases in amount and often contains blood. The pleura may be involved, but this complication definitely is rarer than it is in actinomycosis. The mediastinum is infected almost always, and Baker and Brian have shown that the pericardium and the heart may be invaded. As the disease becomes disseminated, symptoms referable to involvement of other organs appear, such as pain in the bones or prostate or paralyses from invasion of the brain or spinal cord.

A skin ulcer or subcutaneous abscess is often the first symptom suggesting fungus disease. The lesion, which may be of the nodular or gummatous type, starts deep in the corium and develops as a soft subcutaneous nodule varying from 0.5 to 3 cm. in diameter or larger. The overlying skin has a dusky erythematous hue. Such nodules tend to soften, break down and discharge sanguinopurulent material. After rupture, the abscesses may heal, leaving dense depressed scars, or may develop into chronic progressive ulcerative lesions. Ulcerations developed in this way have the same external appearances as those found in cutaneous blastomycosis where the primary site of infection is the superficial layer of the skin. These ulcers have the same type of heaped, finely verrucous borders with abrupt peripheral slope, a zone of dusky violaceous erythema and miliary abscesses. If a subcutaneous abscess is formed by extension from an infected bone, a chronic discharging sinus may develop and persist for months or years.

The PHYSICAL SIGNS of pulmonary blastomycosis resemble those of pulmonary abscess or massive tuberculous infection. Usually there is dulness and the breath sounds are altered, but rales are inconstant and variable in type and distribution. Blastomycosis should be suspected if discharging sinuses or subcutaneous abscesses are present over the thorax or other parts of the body.

X-RAYS.—In rare instances, the early parenchymal lesions may be minimal, the most striking feature being an enlargement of the mediastinal nodes. (Fig. 15.) In most cases, however, the films show dense masses with irregular outlines projecting from the hilum. This type of infection frequently suggests a diagnosis of neoplasm (Fig. 16), especially if the patient also has localized pain in the chest and bloody sputum. In one of our cases, the mass extending from the hilum was thought at first to be an inoperable carcinoma because of destructive processes in two ribs which were diagnosed as metastases. The early lesions are frequently unilateral, but the infection may spread to the opposite side, producing dense shadows in other

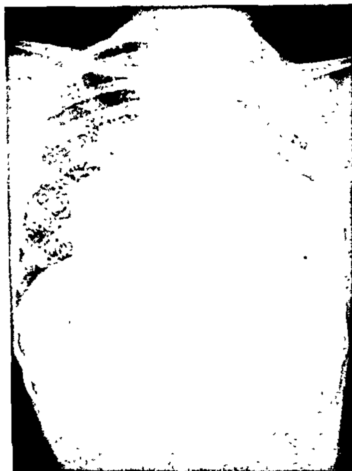


Fig 17.—North American blastomycosis. There is a massive infection of the left lung and nodular miliary-like lesions in the right lung

lung fields. Cavities, when present, are usually small and have irregular, hazy outlines. Sometimes the infection may spread by way of the blood, producing miliary lesions throughout the body. The pulmonary shadows then may resemble miliary tuberculosis except that they are a little coarser and are less well defined. (Fig. 17.)

In disseminated blastomycosis, *roentgenographic examination of* the entire skeleton should be made. The vertebrae and ribs, which are involved most frequently, show a destructive process with some proliferation. As in tuberculosis, the bodies of the vertebrae may be destroyed, resulting in collapse with compression of the spinal cord (Fig. 18.) The lesions are usually less cyst-like than those seen in coccidioidomycosis and less proliferative than those of actinomycosis In many cases a differential diagnosis between these three diseases cannot be made from the x-ray films alone.

*Cutaneous Blastomycosis.—The clinical picture, following inocula*tion of the fungus through the skin, differs markedly from that seen in the systemic disease where the portal of entry is the respiratory tract. Although strains of the fungus isolated from cutaneous blastomycosis are morphologically and immunologically indistinguishable from strains cultured from systemic infections, the latter form of the disease rarely develops in patients with skin lesions of long duration.

In the great majority of cases, the primary skin lesion is found on some exposed part of the body, particularly the face (frontispiece), *hands, wrists, feet or ankles* (Fig. 19.) *The infection* begins as a papule or papulopustule of the superficial skin layer. Breaking down of this lesion is followed by the discharge of purulent or sanguinopurulent material in which the organisms may be found The lesion may crust over, but this is not a prominent sign. The infection spreads slowly by peripheral extension, the contour of *the lesion* often assuming serpiginous or arciform shapes. The central parts of the spreading lesion undergo spontaneous healing, forming scars which show only a slight tendency to contracture. (Fig. 19) The borders of the lesion should be inspected carefully because the diagnosis may be suggested by the characteristic clinical appearance of these active margins. The edges of the lesions are heaped and assume distinctive delicate papilliform or fine verrucous characteristics. These fine verruca are less coarse than those seen in verrucous *tuberculosis cutis and some of the epitheliomas Other differential* characteristics to be noted are the abrupt downward slope of the margins, the dusky violaceous hue at the periphery and the presence of small miliary-like abscesses. The picture at times resembles the lesions of granuloma inguinale



Fig 18 —North American blastomycosis involving the spine Note destruction of the bodies of the vertebrae and the development of a paravertebral abscess

LABORATORY EXAMINATION.—Hypochromic anemia, increased sedimentation rate and leukocytosis with an increase in the neutrophils are common but non-specific findings. The diagnosis cannot be established without the demonstration of the organism, although we have found that either a positive skin test to *Blastomyces* vaccine or a positive complement fixation test justifies a presumptive diagnosis of the infection.

MYCOLOGY

Although different species and varieties of fungi have been described as the etiologic agent of Gilchrist's disease, most investigators are agreed that the disease is caused by a single organism, *B. dermatitidis*. The other described forms are based on cultural and morphologic variations which occur frequently in cultures of all fungi and are of doubtful value as criteria for generic or specific differentiation.

The generic name *Blastomyces* is admittedly an unfortunate one. It had been used previously for an entirely different fungus and, according to the rules of nomenclature, it should be restricted to its first use Also, the term means "budding" which is a phenomenon not only of the tissue phase of the etiologic agent of Gilchrist's disease, but also of fungi belonging to the genera *Saccharomyces*, *Cryptococcus* and *Candida*. Many attempts have been made, therefore, to change the generic name *Blastomyces* but, as yet, there has been no general acceptance of the various names proposed. *Zymonema*, *Gilchristia*, *Blastomycoides*, and so on.

Direct Examination.—Material for microscopic examination is collected from cutaneous lesions by scraping bits of tissue or by obtaining swabs of pus from the undermined, heaped border of the lesion The roof of small abscesses, appearing as tiny white heads around the periphery of the lesion, should be removed and the underlying pus collected. Pus from fluctuant subcutaneous abscesses should be aspirated with sterile needle and syringe. Sputum, urine and spinal fluid should be examined in suspected systemic infections.

The material is examined microscopically by placing a loopful on a slide and gently crushing it to a thin film under a cover glass If cellular debris interferes with the transmission of light, a loopful of material should be mounted in a drop of 10 per cent potassium hydroxide, cover glass added and the preparation gently heated over the low flame of a bunsen burner or alcohol lamp. All preparations should be examined with subdued light from the microscope condenser.

B. dermatitidis appears in these preparations as single or budding spherical cells, 8 to 15 μ in diameter, with a thick refractile wall. This wall is sufficiently thick to give these forms a "double-contoured" appearance in fresh preparations. No mycelium is present. (Fig. 20.)

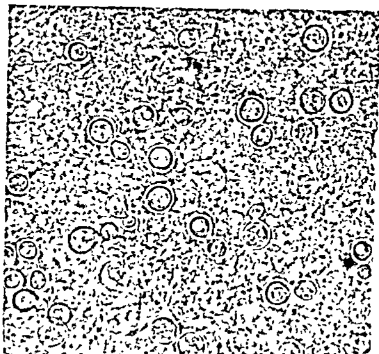


Fig. 20.—*Blastomyces dermatitidis.* Round, double-contoured, budding yeastlike cells in pus from subcutaneous abscess. × 700.

Cultures.—The infected material (pus, bloody discharges, sputum or spinal fluid) should be cultured on blood agar or beef infusion glucose agar to be incubated at 37° C. and on Sabouraud's glucose agar slants to be incubated at room temperature.

On blood agar or beef infusion glucose agar at 37° C., the fungus grows slowly and develops wrinkled, waxy colonies. (Fig. 21 *A*.) Microscopic examination shows the colony to be composed of budding yeastlike cells identical with those seen in infected material from lesions and short mycelial fragments suggesting an attempt on the part of the fungus to develop into a mycelial phase of growth. (Fig. 21 *B*.)



Fig 21 —*Blastomyces dermatitidis* *A* Yeastlike culture, twenty-one days, on beef infusion glucose agar at 37° C *B* Budding yeastlike cells from beef infusion glucose agar at 37° C. × 700

On Sabouraud's glucose agar at room temperature, the mycelial phase of the fungus predominates, finally developing a white, cottony aerial growth which becomes tan to brown with age. (Fig. 22 *A*) When first cultured from the infected material, however, it tends to remain yeastlike for a short period of time, during which the mycelium is broad, thick-walled and closely septate, giving the general appearance of a *Geotrichum*. (Fig. 47 *B*.) Hyphal projections (coremia) develop from the surface, accounting for the so-called "prickly stage" of growth. Later the entire surface becomes overgrown with a white aerial mycelium which gradually develops the changes noted above. Microscopically, these fully developed cultures show numerous oval to round conidia, 3 to 4 μ in diameter, attached to the hyphae near septations; other round to pyriform conidia, 4 to 5 μ in diameter, are borne on lateral sterigmata of varying lengths. In old cultures many chlamydospores are developed, 7 to 18 μ in diameter, with outer walls thickened to give unusual appearances The mycelial phase can be converted to the yeastlike phase by subculturing the organism to fresh media and incubating the cultures at 37° C.

Animal Inoculation.—Infected material from the lesions can be inoculated intraperitoneally into guinea pigs or mice. Saline suspensions of pure cultures, either the yeastlike phase grown at 37° C. or the mycelial phase grown at room temperature, may be injected intraperitoneally into mice. Typical lesions should develop in mice in 3 weeks with gross infection of the liver, spleen, lungs and lymph nodes Microscopic examination of fresh material from these lesions or the peritoneal fluid will show readily the yeastlike budding tissue forms of the fungus.

Mycologic Diagnosis.—Direct microscopic examination of material from lesions should reveal the large, spherical, thick-walled budding forms of the fungus. When cultured, the fungus develops as a yeastlike organism (tissue form) at 37° C or as a filamentous moldlike organism at room temperature. It is similar to *B. brasiliensis* in that this fungus also produces a yeastlike and moldlike culture at 37° C. and room temperature respectively. They differ microscopically, however, in the yeastlike phase *B. dermatitidis* produces a single bud from the parent cell, whereas *B. brasiliensis* produces multiple buds from the surface of the parent cell *B dermatitidis* differs from *Cryptococcus neoformans* in that cultures of the latter remain yeastlike regardless of the temperature at which grown

A



Fig 22.—*Blastomyces dermatitidis* *A* Filamentous colony on Sabouraud's glucose agar, twenty-three days, at room temperature *B* Round and pyriform conidia found in filamentous stage from Sabouraud's glucose agar at room temperature. × 700

Blastomyces dermatitidis Gilchrist and Stokes, 1898. Synonymy.—*Oidium dermatitidis* Ricketts, 1901; *Cryptococcus Gilchristi* Vuillemin, 1902; *Zymonema Gilchristi* Beurmann and Gougerot, 1909; *Glenospora Gammeli* Pollacci and Nannizzi, 1927; *Blastomycoides tulanensis* Castellani, 1928; *Endomyces capsulatus* Dodge and Ayers, 1929; *Monosporium tulanense* Agostini, 1932; *Glenospora brevis* Castellani, 1933; *Endomyces capsulatus var. isabellinus* Moore, 1933; *Zymonema dermatitidis* Dodge, 1935; *Zymonema capsulatum* Dodge, 1935.

PATHOLOGY

In either generalized or cutaneous blastomycosis, the most characteristic reaction to the organism is abscess formation although chronic inflammation with giant cells, necrosis and fibrosis may predominate. In cutaneous lesions, the most common and characteristic finding is the presence of numerous abscesses of almost microscopic size. In old lesions, all the signs of chronic inflammation and scarring are present. In some instances the epithelial hypertrophy may be so marked as to suggest carcinoma. The systemic form of the disease is usually a pyemia; but in certain cases there may be caseous necrosis of tissue and tubercle formation, making it difficult to distinguish this disease from tuberculosis. Osteomyelitis due to *B. dermatitidis* may be encountered in routine study of tissue removed surgically, and must be differentiated from other forms of osteomyelitis

Biopsy.—Biopsy of the edge of a lesion of cutaneous blastomycosis shows *extraordinary hypertrophy and hyperplasia of the epidermis* due to the chronic inflammatory reaction incited by the fungus (Fig. 23) The reaction consists of minute abscesses (Fig. 24 *A*) in which the yeastlike organisms may be found lying free. The polymorphonuclear neutrophil is the predominant cell found about the organisms, but macrophages and fibroblasts predominate in the periphery of the abscess and organisms may be found in the cytoplasm of giant cells The abscesses are both intradermal and intraepidermal, the latter representing hyperplasia of the epidermis about sinuses extending from dermal abscesses

The finding of these abscesses in sections showing chronic inflammation is highly suggestive of blastomycosis, and careful search for the organisms should be made. In sections stained with hematoxylin and eosin, the fungus appears as a rounded structure with thick

walls, giving a double-contoured appearance. (Fig. 24 *B*.) There is a central mass of material which stains with variable intensity. This central mass also stands out sharply when stained by Gram's method.

Biopsies from the subcutaneous tissues and bone usually show the organisms in great numbers. Masses of necrotic organisms and pus cells mixed with red blood cells account for the characteristic pinkish color of the pus from subcutaneous abscesses. The pathologic reaction in blastomycotic osteomyelitis is essentially the same as that observed in subcutaneous abscesses.



Fig 23 —Cutaneous blastomycosis Extraordinary epidermal hyperplasia and hypertrophy to right where dermal and epidermal abscesses lie Epidermis of normal thickness to left, subcutaneous fat below Very low magnification.

Fig 24 —Cutaneous blastomycosis *A* Typical minute abscess in corium with double-contoured organism in center Giant cells at periphery H & E. × 175. *B* Budding blastomycete with thick capsule in giant cell H & E. × 1500

Blastomycosis may be encountered in enlarged lymph nodes removed for diagnosis and in endometrial curettings and resected tubes

Blastomycosis in the resected lung may resemble grossly carcinoma of the lung, and the distinction between the two may be difficult until histologic studies are made.

Autopsy.—The lesions found at autopsy in four cases of systemic blastomycosis are illustrated in Fig. 25. Infection of the lungs is present regularly in patients dying of systemic blastomycosis. The pulmonary lesions may vary from scattered small nodules to larger caseous nodules and abscesses. Cavities are infrequent but do occur. (Case 2.) An active pleurisy or pleural fibrosis usually is encountered, and there may be pericarditis. Congestive heart failure can result from pericardial pus or from pericardial adhesions. Direct extension from the pleural cavity to ribs or to the surface of the chest is not rare. In the systemic disease, it is common to find infection of some portion of the skeleton with sinuses draining to the surface or to subcutaneous abscesses. Isolated abscesses may be found in muscle, and psoas abscesses, simulating tuberculosis, are not infrequent. Prostatic abscesses are frequent in the male, and blastomycosis of the tubes and uterus may occur in the female. Abscesses of the brain and meningitis may develop during the course of the disease Lymph nodes may be changed to conglomerations of abscesses, areas of necrosis and fibrosis. Cutaneous lesions in the systemic disease are almost identical with those in cutaneous blastomycosis except that more organisms usually are present. Involvement of the spleen, liver and kidneys may be remarkably slight in the presence of widespread skeletal and subcutaneous blastomycosis In other cases, great numbers of small hematogenous tubercles or minute abscesses may be present in the liver, spleen and kidneys

The histologic reaction in cases studied at autopsy is usually that of chronic suppuration, necrosis or fibrosis In some areas the organisms cannot be demonstrated

IMMUNOLOGY

Serology.—The sera of patients with extensive blastomycotic lesions will fix complement specifically with supsensions or extracts of *B. dermatitidis* There is no cross-reaction with other fungus antigens, and the reaction is always negative in the absence of blastomycosis. In patients with extensive systemic involvement, complete

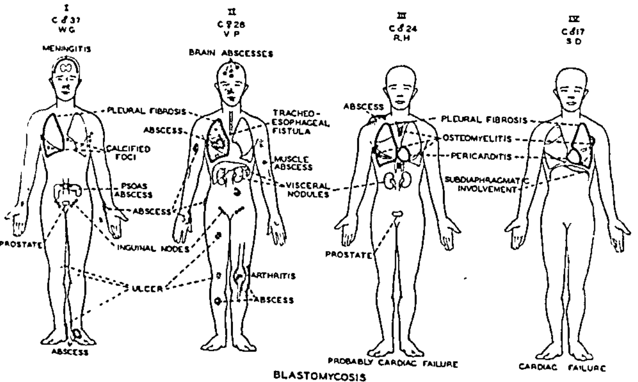


Fig. 25.—The distribution of lesions in four cases of blastomycosis studied at autopsy. (After Baker, American Journal of Pathology, *18*.)

fixation occurs in high serum dilutions, but no fixation occurs in undiluted sera of patients with the localized cutaneous form of the disease. The failure to demonstrate antibodies in mild infections probably results from the use of an antigen possessing relatively low combining powers. No attempt has been made to increase the sensitivity of the antigen because the diagnosis of cutaneous blastomycosis by direct examination and culture is not difficult and false positive reactions might be obtained in uninfected patients. The antibody titer is of prognostic significance when correlated with the degree of hypersensitivity of the patient. (Table I)

By the complement fixation technic, it has been shown that sera from patients with blastomycosis fix complement with strains of *B. dermatitidis* isolated from other sources, as well as with strains of *Blastomyces* studied elsewhere and identified as *Glenospora*, *Blastomycoides*, *Monosporium* and *Endomyces*.

Hypersensitivity.—Most patients with blastomycosis are hypersensitive to the fungus or fungus products, as shown by skin tests with vaccines or *Blastomyces* extracts. The reaction is of the tuberculin type, resulting in maximal erythema in twenty-four to forty-eight hours, followed by the formation of small sterile abscesses in very hypersensitive patients. The carbohydrate fraction produces its maximal reaction in twenty-four hours, and the protein material causes a reaction similar to that produced by vaccine except that abscess formation never occurs Positive reactions have not been observed in patients without blastomycosis, but negative reactions can occur in patients with widespread disease

There are no data concerning the stage of the disease at which the positive skin test develops since patients rarely are seen early in the infection Skin tests become negative during the terminal phases of infection, suggesting a state of anergy

DIFFERENTIAL DIAGNOSIS

Systemic blastomycosis must be differentiated from tuberculosis, syphilis, neoplasm, lung abscess, sarcoidosis, silicosis, osteomyelitis, pyemia and psoas abscess, as well as other fungus infections, namely, coccidioidomycosis, actinomycosis, cryptococcosis, South American blastomycosis, sporotrichosis and moniliasis

Cutaneous blastomycosis may simulate verrucous tuberculosis, epithelioma, bromoderma, iododerma, nodular ulcerative syphilids, granuloma inguinale and other granulomata

TABLE I: SUMMARY OF IMMUNOLOGIC FINDINGS IN 22 CASES OF BLASTOMYCOSIS

PATIENT	COMPLEMENT FIXATION TITER	SKIN TEST TO VACCINE	TYPE OF LESIONS	OUTCOME
	Group 1		*Complement fixation positive*	*Skin test negative*
S. D.	1:32	Neg	Generalized	Died
E. L.	1:32	Neg.	Generalized	Died
R. M.	1:32	Neg.	Generalized	Disease progressing
V. P.	1:16	Neg.	Generalized	Died
W. M.	1 16	Neg.	Primary in skin; later developed abdominal mass	Unknown
S C	1:32	Not done	Outside case; no details	Prognosis considered hopeless by attending physician
R. H.	1:32	1 plus	Generalized	Died
	Group 2		*Complement fixation positive*	*Skin test positive*
V. S.	1:16	2 plus	Lungs, peritoneum, bones	Cured
I. B.	1:8	2 plus	Skin (extensive)	Markedly improved
R. R	1·2	3 plus	Skin of foot	Markedly improved
U. W.	1:2	2 plus	Bone	Markedly improved
	Group 3		*Complement fixation negative*	*Skin test positive*
A. J	Neg.	2 plus	Skin (face)	Markedly improved
B. V	Neg.	2 plus	Skin (subcut. abscess)	Markedly improved
N A.	Neg	3 plus	Skin	Improved; recurrence 4 years later
A. M	Neg	3 plus	Skin	Cured
H. L	Neg	4 plus	Skin	Cured
A Y.	Neg	4 plus	Lungs (subcut abscess)	Cured
F M.	Neg.	2 plus	Skin	Not followed
N. G	Neg	1 plus	Skin	Not followed
G. D.	Neg	2 plus	Lungs and skin	Cured
M F.	Neg	2 plus	Subcutaneous tissue	Cured
	Group 4		*Complement fixation negative*	*Skin test negative*
P. S.	Neg.	Neg.	Skin	Not followed
G J.	Neg.	Neg	Skin (very extensive)	Died
H M	Neg	Neg. (serum test positive)	Bones	Cured after serum therapy

PROGNOSIS

Systemic blastomycosis usually is fatal. In their review of the literature, Martin and Smith noted a mortality rate of 92 per cent in patients who had been followed for 2 years or longer. Cutaneous blastomycosis rarely causes death, and untreated lesions may be present for many years.

In evaluating prognosis, immunologic data are very helpful. (Table J.) A fatal outcome is to be expected in patients with a high antibody titer (indicating extensive disease) and a negative or slightly positive skin test (indicating anergy). The prognosis is best in the hypersensitive patient without complement fixing antibodies in his serum

TREATMENT

Potassium iodide was used successfully by Gilchrist in the treatment of his early cases of cutaneous blastomycosis, and oral administration of this drug has been accepted as the most reliable method of therapy in both the cutaneous and the systemic forms of the disease Although iodides are curative in some cases of blastomycosis, only temporary improvement has been attained in others Furthermore, administration of the drug sometimes has an adverse effect, resulting in a spread of the infectious process. Best results are obtained when iodide therapy is supplemented by the judicious use of x-ray therapy, suitable surgical procedures and desensitization with vaccines

Systemic Blastomycosis.—It is essential that the patient be supported by all of the general measures used in the treatment of tuberculosis, actinomycosis or any other severe systemic disease, namely bed rest and a good diet supplemented by potent vitamin preparations.

A skin test should be done on every patient before any course of therapy is outlined. The skin test is performed by the intracutaneous injection of 0.1 cc. of a standardized heat-killed *Blastomyces* vaccine. (The preparation of this material is described in the Appendix.) The site of injection should be observed at twenty-four and forty-eight hour intervals to determine the size of the maximal reaction If the erythematous reaction is less than 1 cm in diameter, it is safe to administer potassium iodide by the rapid method outlined below A reaction 1 cm. or more in diameter indicates hypersensitivity, and the patient should be desensitized. The desensitization

filtered through 1 mm. Al, at weekly intervals; and the total dose should not exceed 1200 to 1500 roentgen units. Overtreatment is the most common error; small doses are adequate for the patient who has had a previous course of vaccine therapy.

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Chapter III

COCCIDIOIDOMYCOSIS

(*Coccidioidal Granuloma, Valley Fever, Desert Rheumatism, San Joaquin Fever, Posada-Wernicke's Disease*)

COCCIDIOIDOMYCOSIS is probably the most infectious of the systemic mycoses; the majority of individuals who live in endemic areas for any length of time acquire the infection.

Definition.—Coccidioidomycosis is an infectious disease, caused by *Coccidioides immitis*, which presents a variety of clinical manifestations. Infection may result in: (1) PRIMARY COCCIDIOIDOMYCOSIS, which usually is an acute but benign, self-limited respiratory disease; or (2) PROGRESSIVE COCCIDIOIDOMYCOSIS, which is a chronic, malignant and disseminated disease involving cutaneous, subcutaneous, visceral and osseous tissues.

Geographic Distribution.—Although the first case of infection with *C. immitis* was reported from Argentina, only two other authenticated cases and a possible fourth case have been described from South America. The other South American cases reported as coccidioidomycosis are recognized now as infections caused by an unrelated fungus [illegible]

[illegible]

region since many cases [illegible]
New Me [illegible]
in Arizc [illegible]
children react positively to coccidioidin, indicating almost universal [illegible]

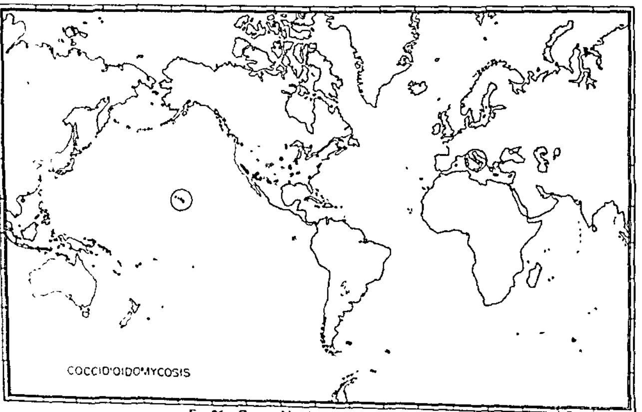


Fig. 26.—Geographic distribution of coccidioidomycosis.

from contact with soil contaminated with the fungus. Strains of *C. immitis*, pathogenic for animals, have been cultivated from samples of soil found in endemic areas, and it is thought that the fungus is breathed into the lungs with dust or introduced into the skin following an injury.

Naturally occurring infections have been found in cattle, sheep and dogs, but it is unlikely that man acquires the infection from animal sources. Emmons suggests that coccidioidomycosis is an [illegible]
primarily an animal pathogen and that contamination of the soil is maintained by such infected rodents.

[illegible]
cidioidomycosis is found to affect both sexes equally, the progressive granulomatous type of infection is found most frequently in males, in one series of 212 cases, 176 of the patients were males. The pro- [illegible]
from old dry cultures

SYMPTOMATOLOGY

The symptoms and signs of primary coccidioidomycosis and progressive coccidioidomycosis are so different that they are best considered as separate clinical diseases although the same fungus causes both types of infection. The *primary infection* is subdivided further because the symptomatology is dependent upon the portal of entry of the fungus.

Primary Pulmonary Coccidioidomycosis.—The organism is inhaled with dust in endemic areas, and symptoms, if they develop, appear after an incubation period of 10 to 14 days Many infections are subclinical, however, as proved later by positive coccidioidin skin tests. The symptoms usually are those of a mild upper respiratory infection, such as low grade fever (99° to 101° F.) and a slight nonproductive cough. Other patients have chills, night sweats, anorexia



Fig. 27.—Primary coccidioidomycosis of the lungs. The patient had skin lesions resembling erythema nodosum when this picture was made. Note enlarged hilar lymph nodes and wedge-shaped lesion in left lung. (Courtesy of Dr. C. E. Smith.)

backache and headache. Small amounts of mucopurulent sputum, which is occasionally blood streaked, may be raised. In rare instances, the initial symptoms are those of pleurisy with effusion, but more often a dry type of pleurisy results and the patient complains of a sensation of constriction in the upper chest. At times there is severe continuous pain, resembling that caused by coronary occlusion, fractured rib or nephrolithiasis. Physical examination usually reveals nothing more than a mild nasopharyngitis. Abnormal findings in the lungs may be difficult to demonstrate even when pleuritic pain is present. In the more severe infections, there may be dulness and suppressed breath sounds and rales can be elicited.

SYMPTOMS.—The initial symptoms usually subside in 1 or 2 weeks; but in about 3 per cent of the cases, allergic manifestations appear 3 days to 3 weeks after the termination of the febrile period. Fever reappears and numerous tender nodular lesions, resembling ERYTHEMA NODOSUM, develop, usually over the shins but occasionally they are found scattered over the arms, thighs, buttocks and scalp. After 2 or 3 days, the tenderness subsides and the lesions begin to fade, leaving brownish pigmented areas which may persist for several weeks. In rare instances, a second crop of nodules may appear after an interval of weeks. Lesions resembling ERYTHEMA MULTIFORME may appear on the margins of the palms, face, neck and upper extremities whether or not ERYTHEMA NODOSUM is present. An occasional patient may develop phlyctenular conjunctivitis or acute arthritis, especially of the knees and ankles. The joints usually are



different types of reaction, and more than one type may be found in a single patient. To avoid confusion, the various roentgenographic changes will be discussed separately

1. The films may show nothing but SOFT, FUZZY HILAR THICKENINGS, resembling the early lesions of almost any type of pulmonary infection. Such lesions usually clear in 1 to 2 weeks

2 The

MONIC

enous

lower lung fields (Fig. 27.) Most often these shadows disappear in



Fig. 28.—Primary coccidioidomycosis of the lungs. Note the thin-walled cavity in the apex of the left upper lobe.

a week or 10 days after the clinical symptoms have subsided, but they may persist for months

3. The most characteristic finding is that of well-isolated and well-circumscribed NODULAR LESIONS in the parenchyma of the lung. Such nodules are 2 to 3 cm. in diameter and occur most often in the middle or lower lung fields; they usually occur singly, but sometimes they are multiple and resemble metastatic foci or the nodules of primary tuberculosis. Such lesions are benign in character, and after a period of months they either resolve or develop into thin-walled cyst-like cavities. (Fig. 28.) Such cavities may disappear or shrink to small, fibrous nodules which subsequently may become calcified. Large cavities, however, may persist for several years

4. MEDIASTINAL and HILAR ADENOPATHY is relatively infrequent in primary coccidioidomycosis, but may be seen in association with parenchymal infiltration in the more acutely ill patients In rare instances, such enlargement is the only finding and the infection may be confused with Hodgkin's disease or some other form of mediastinal growth

5 Small PLEURAL EFFUSIONS, sufficient in amounts to obscure the costophrenic angle, occur in about one-fifth of the cases. Such effusions absorb rapidly and completely; massive effusion is rare.

Non-pulmonary Primary Coccidioidomycosis.—This type of infection occurs frequently on the exposed surfaces of the skin, but it may appear in the neck region Rixford reported an instance in a laborer who developed a verrucous growth on the back of his neck where his collar band had rubbed The lesion remained localized for 8 years, and then spread to other parts of the body In Guy and Jacob's patient, the organism presumably was introduced [illegible] thumb following the prick of a cactus thorn [illegible] at the site of the injury foll[illegible] developed alon[illegible] glands were rea[illegible] e [illegible] 1 [illegible] also is seen in sporotrichosis

More often, the primary skin lesion is not associated with obvious trauma, but begins as a painless, solid nodule A pink to dusky red discoloration of the skin develops, the lesion ulcerates and exudes a thick, mucoid, grayish yellow pus in which the organisms can be found Such ulcers are necrotic and indolent and, after a few weeks or months, may become papillomatous and resemble fungating epitheliomas Primary lesions on the nose or face may spread to the central nervous system and result in the development of an acute or



Fig. 29 —Progressive coccidioidomycosis. Note large subcutaneous abscess and one draining sinus.

subacute meningitis Under favorable conditions, primary cutaneous lesions may resorb, leaving depressed and atrophic, but fairly pliable, scars.

The SCROFULODERMIC TYPE, first noted in the superficial lymph nodes of the neck, may result from primary invasion through the mucosa of the nasopharynx in a manner analogous to the chain of events resulting in tuberculous adenitis. That the infection can be introduced through the mucous membranes is illustrated by Ahlfelt's experiment, which showed that guinea pigs could be infected by rubbing the organisms into artificially produced abrasions on the oral mucous membrane. The disease may become generalized and involve the internal organs; or the sinuses, after draining for months, may heal with scar formation.

LABORATORY EXAMINATION.—The blood count during the first week of the disease shows an initial leukocytosis, followed by a definite increase in the eosinophils The sedimentation rate is elevated during the first phase of the primary infection, but returns to normal when the infection subsides. A persistence of an elevated sedimentation rate suggests that the patient is developing the progressive type of coccidioidomycosis, and determination of the sedimentation rate is, therefore, of considerable help in evaluating the clinical significance of a positive coccidioidin skin test. If the sedimentation rate is normal, one may assume that the primary infection occurred sometime in the past; but if it is elevated, the patient either is ill with his primary infection or he is developing the progressive form of the disease.

Precipitin and complement fixing antibodies are absent in mild cases but appear in the more severe primary infection, only to disappear with recovery. In some of the patients with cavities of long duration, the complement fixing antibodies disappear completely, but in others they persist at a low level.

Progressive Coccidioidomycosis.—A recent and extensive study of cases of primary coccidioidomycosis occurring in Army camps in the Southwestern part of the United States shows that only about 0 2 per cent of the cases of primary infection develop into the progressive, and usually fatal, form of the disease. The patient who is destined to develop the malignant form of the disease usually shows evidence of dissemination of infection throughout the body within a period of weeks or months after the onset of the primary infection. In other instances, there is a period of improvement following the initial infection, and for a period of 5 to 6 months the patient is well enough



Fig 30.—Progressive coccidioidomycosis of the lungs The patient died of the disease (Courtesy of Dr C E. Smith)

to be ambulatory but unable to work. A few cases of progressive coccidioidomycosis have been reported in patients who had, 5 to 10 years before, recovered from "valley fever," "desert fever," "desert rheumatism," "San Joaquin fever" or "the bumps," now interpreted as synonymous with the ERYTHEMA NODOSUM phase of the primary infection Only time will reveal whether more of the 499 out of 500 primary infections eventually will develop the disseminated form of the disease.

The progressive type of coccidioidomycosis may terminate fatally within a few months, or the patient may live for a year or more. The patient has a continuous low grade fever and marked anorexia, and rapidly loses weight and strength. Dyspnea appears and cyanosis may be extreme as the pulmonary infiltration increases. The physical signs in the chest are those of dulness and altered breath sounds; rales are inconstant and variable. However, no physical signs may be found in some patients who have large areas of consolidation as shown by roentgenographic examination The sputum is mucopurulent and usually contains many of the characteristic fungus spherules. The sputum may contain blood, but it is a less common finding in coccidioidomycosis than it is in tuberculosis and some of the other mycoses. As the disease progresses, invasion of the bones, joints, skin, subcutaneous tissues (Fig. 29), internal organs, brain and meninges may occur. If MILIARY DISSEMINATION occurs, the patient develops high fever with chills, profuse sweats and marked prostration and death may occur within a few weeks

COCCIDIOIDAL MENINGITIS is found at necropsy in approximately 25 per cent of the cases Recently Abbott and Cutler reported a study of seven instances of chronic coccidioidal meningitis in which they could find no clinical evidence pointing to an original focus of infection The symptoms were those of chronic meningitis, but some patients also had symptoms of obstructive hydrocephalus. There was a low grade fever and a moderate leukocytosis with an increase in neutrophils There was frequently a positive colloidal gold reaction of the meningitic type.

X-RAYS.—If the primary pulmonary infection persists for 5 or 6 weeks, the progressive form of the disease should be suspected. The development of progressive coccidioidomycosis from the primary form can be suspected by roentgenographic examinations (1) if ACUTE PROGRESSIVE PULMONARY CONSOLIDATION appears (Fig. 30), (2) if TUBERCULOUS-LIKE INFILTRATIONS with clouding, mottling, fibrosis and cavitation appear at the apices or in the subapical areas,



[illegible] like destructive [illegible] Program for [illegible] W. Eighth [illegible]

(3) if MEDIASTINAL ADENOPATHY is present to a marked degree, or (4) if BONE OR JOINT INVOLVEMENT occurs

The typical lesion in bone is that of a sharply circumscribed area of destruction with little or no reaction in the surrounding bone. (Fig. 31.) Such lesions are cystlike in appearance and vary from 0.5 to 3 cm. in diameter. Sometimes a proliferative periostitis occurs with or without destructive changes in the subjacent bone. Although any bone in the body may be involved, those most frequently invaded are the ribs, vertebral bodies, small bones of the hands and feet, tibial tubercles, malleoli, olecranon, styloid processes, acromial processes and the angles of the scapulae. Joints may be involved by direct extension from subarticular foci, giving a picture resembling that of a tuberculous lesion. MILIARY DISSEMINATION produces lesions which resemble miliary tuberculosis although the individual shadows tend to appear more fuzzy in outline.

LABORATORY EXAMINATION.—Blood counts show a hypochromic [illegible]

[illegible]

precipitin and complement fixing antibodies are high, but the coccidioidin skin test frequently becomes negative in the terminal phases of the infection.

MYCOLOGY

Coccidioidomycosis is caused by a single species of fungus, *C. immitis*.

Direct Examination.—In suspected cases, sputum, gastric contents, pleural fluid, pus from subcutaneous abscesses and exudates of cutaneous lesions should be examined microscopically. Such materials should be examined unstained under subdued light after making a thin cover glass preparation. Scrapings from lesions should be cleared in a drop of 10 per cent potassium hydroxide

C. immitis appears in infected materials as a non-budding, spherical, thick-walled structure, 20 to 80 μ in diameter, which is filled with numerous small (2 to 5 μ in diameter) endospores (Fig. 32.) In tissues, the fungus reproduces by means of these endospores which are freed by rupture of the cell wall Such bodies increase in size and develop into the typical large endospore-containing spherule. At times, immature cells containing none or only a few endospores [illegible]

[illegible]



Fig. 31.—Progressive coccidioidomycosis of foot Note the cyst-like destructive lesion of the bones. (After syllabus "Coccidioidomycosis Control Program for the A.A F W F.T.C.," No 710, from the Office of the Surgeon, 1104 W Eighth St, Santa Ana, California)

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Cultures.—Suspected materials should be planted on Sabouraud's



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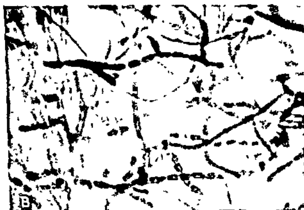


FIG. 33.—*Coccidioides immitis*: *A* Culture on Sabouraud's glucose agar, nineteen days, at room temperature *B* Segmentation of hyphae into oblong, thick-walled arthrospores from Sabouraud's glucose agar culture at room temperature × 600

glucose agar or beef infusion glucose agar slants and incubated at room temperature. On such media the organism develops at first as a *moist, membranous colony which appears to be closely applied to* the surface of the agar. However, the organism quickly develops an abundant cottony aerial mycelium which is white at first but becomes tan to brown with age. (Fig. 33 *A*.) Microscopically, these cultures show branching, septate hyphae which break up into numerous thick-walled, rectangular, ellipsoidal or spherical arthrospores about 2.5 to 3 by 3 to 4 μ in size. (Fig. 33 *B*) Extreme caution should be exercised when transferring or examining the growth from these cultures since the arthrospores are highly infectious



Fig. 32.—*Coccidioides immitis* Round, thick-walled, endospore-filled spherule and collapsed spherule in pus $\times$ 700

Animal Inoculation.—The injection of infected material into the testes of guinea pigs results in the development of a severe orchitis within 7 to 10 days. Pus aspirated from such *swollen testes* shows the organisms as typical spherules filled with endospores. Mice, also, can be infected by the intraperitoneal injection of saline suspensions of the mycelial forms obtained from culture

Mycologic Diagnosis.—In direct examination of tissue, the young immature forms of *C. immitis* may not contain endospores and may be confused with non-budding immature forms of *B. dermatitidis*. The specimens should be searched carefully for the diagnostic endospore-filled mature forms.

In culture, this fungus must be differentiated from *Geotrichum*, which also produces arthrospores by segmentation of hyphal strands. *C. immitis* always grows as a mold on Sabouraud's medium, in contrast to *Geotrichum* which remains moist and yeastlike.

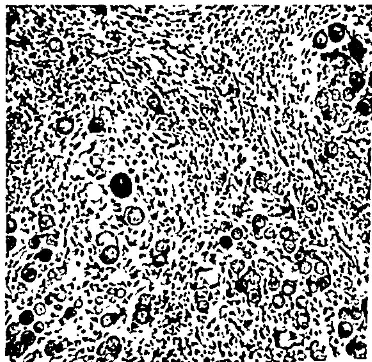


Fig. 34.—Coccidioidal granuloma. Lymph node with much scarring. The spherules are largely in a stage which does not show the endospores. H. & E. × 1200

Coccidioides immitis Rixford and Gilchrist, 1896. Synonymy.—*Posadasia esferiformis* Cantón, 1898; *Blastomycoides immitis* Castel- [illegible] *Geotrichum* [illegible] 932, [illegible] *lerum* [illegible] Castellani, 1933.

COCCIDIOIDOMYCOSIS

PATHOLOGY

The pathologic lesions in progressive coccidioidomycosis are almost identical with those seen in North American blastomycosis, and it is not strange that these two diseases were confused at first. Both have extensive skin lesions, subcutaneous pockets of pus, extensive involvement of the skeleton and both exhibit similar lesions of the internal organs.

Biopsy.—CUTANEOUS LESIONS show polymorphonuclear abscesses in which the organisms occur free or can be found in large numbers within giant cells and in the adjacent granulation tissue. Epithelial hypertrophy and hyperplasia occur as a result of the chronic inflammatory process.

In LYMPH NODES, there may be abscesses and nodules of fibrous tissue with giant cells, many of which contain the parasites. (FIG. 34) The majority of organisms are practically indistinguishable from the non-budding forms of either North or South American blastomycosis. (FIG. 35 *A*.) Such forms have a thick, double-contoured wall, and the material within the cell wall stains in an irregular fashion In general, at this stage of development, the fungus tends to take the stain more densely just beneath the capsule than does the organism of North American blastomycosis, but the difference is too slight to be of diagnostic import. The diagnosis of coccidioidomycosis is made by finding the endosporulating organisms (FIG. 35 *B*, *C*)

The HISTOLOGIC APPEARANCE of tissue from the subcutaneous abscesses is similar to that seen in bone infections. In bone, necrosis and abscess formation are conspicuous, but there may be cavities filled with granulation tissue instead of abscesses Nodules from the brain, removed in the course of a craniotomy, have been shown by biopsy to be due to *C. immitis*.

Autopsy.—Subcutaneous abscesses and foci in bones, testes and meninges are conspicuous at autopsy Subcutaneous abscesses or areas of osteomyelitis often connect with the skin surface by sinuses. In the lungs, abdominal organs and internal lymph nodes there may be areas of necrosis and abscesses Tubercle-like structures are present in the viscera, resulting from hematogenous spread of the organism The testicular tissue frequently is involved. In any portion of the lungs there may be extensive caseous pneumonia with abscess formation. Cavities may be present, but they do not occur as frequently as they do in tuberculosis





Fig 35 —Coccidioidal granuloma: *A* Giant cell containing a rounded, thick-walled form easily confused with similar forms in North and South American blastomycosis Lymph node Case of fatal coccidioidal granuloma H & E × 1200 *B*. Endosporulating spherule in an abscess of a lymph node H & E × 1200. *C*. Endosporulating spherule ruptured on one side Note the peripheral spines. From same lymph node H & E × 1200

IMMUNOLOGY

Serology.—Complement fixation and precipitin tests are positive in patients with severe infections but usually are absent in very mild cases. As in North American blastomycosis, the antibody titer is highest in patients with the most extensive involvement; a rise in [illegible]

[illegible]

The development of an area of erythema or induration of 0 5 cm. or larger is considered a positive test. Tests must be interpreted in the same manner as are tuberculin tests; i e., a positive test indicates simply that infection by *C. immitis* has occurred at sometime during the patient's life. As in North American blastomycosis, the patient may become anergic as the lesions become widespread, and a negative coccidioidin test to a 1:10 dilution is not unusual in the terminal stages of the infection

DIFFERENTIAL DIAGNOSIS

Coccidioidomycosis should be suspected in every obscure illness originating in a person living in an endemic area or in individuals who have visited such areas at any time.

Primary coccidioidomycosis may be diagnosed incorrectly as common cold, bronchitis, influenza, bronchial pneumonia or primary atypical pneumonia of unknown etiology.

Progressive coccidioidomycosis must be differentiated from tuberculosis, syphilis, glanders, tularemia, bacterial osteomyelitis, neoplasms and other mycoses, particularly blastomycosis, actinomycosis, cryptococcosis, sporotrichosis, histoplasmosis and mycetoma

PROGNOSIS

The prognosis is excellent in primary pulmonary coccidioidomycosis and is good in the cutaneous and glandular types of primary infection. In the internal and meningitic types of coccidioidomycosis, the prognosis is very grave.

TREATMENT

Patients with primary coccidioidomycosis should be kept in bed until their temperature, white blood count and sedimentation rate are normal Before the patient is discharged, the physical signs should have subsided and the x-rays should show either normal findings or progressive clearing With conservative treatment, residual

cavities usually heal over a period of months. An occasional case complicated by hemoptysis may require pneumothorax, and, if this is not successful, a thoracoplasty or a lobectomy should be considered.

Progressive coccidioidomycosis is very resistant to treatment. Arsphenamine, crystal violet, gentian violet, thymol and other related oils, copper, antimony and potassium tartrate intravenously, sulfonamides and iodides all have been tried without success.

Although the prognosis is almost hopeless, a few recoveries have been reported. Every effort should be made to support the general resistance of the patient by rest in bed and a good diet, supplemented by liver extract and all the known vitamins.

Martin and Smith have shown that cases of blastomycosis that have developed a marked sensitivity to the products of the fungus are resistant to therapy and may grow rapidly worse when treated with potassium iodide. If these patients are desensitized by gradually increasing doses of the *Blastomyces* vaccine, improvement can be accelerated by potassium iodide therapy. Since hypersensitivity to coccidioidin is such a striking feature in the early stages of progressive coccidioidomycosis, it would seem a logical procedure to desensitize the patient with coccidioidin, following the schedule and dosage outlined in the section on treatment of blastomycosis. Jacobson has recommended the use of a special extract of the organisms, prepared by mixing equal parts of the filtrate from a broth culture and the filtrate from the macerated organisms. Jacobson treated thirty patients over a period of 5 years by injecting the special extract described above, supplemented by intragluteal injections of 5 cc. of colloidal copper. Improvement was noted in a number of cases, and some cures were obtained.

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Chapter IV

SOUTH AMERICAN BLASTOMYCOSIS

(*Paracoccidioidal Granuloma, Lutz-Splendore-De Almeida's Disease*)

THIS DISEASE, apparently limited to South America, is referred to most often as paracoccidioidal granuloma because the tissue form of the fungus causing the infection has some resemblances to the organism causing coccidioidomycosis. Recent studies have shown that the fungus reproduces by budding and, consequently, it seems better to include the disease among the blastomycoses

Definition.—South American blastomycosis is a chronic granulomatous disease of the skin, mucous membranes, lymph nodes and internal organs caused by *Blastomyces brasiliensis*.

cavities usually heal over a period of months. An occasional case complicated by hemoptysis may require pneumothorax, and, if this is not successful, a thoracoplasty or a lobectomy should be considered.

Progressive coccidioidomycosis is very resistant to treatment Arsphenamine, crystal violet, gentian violet, thymol and other related oils, copper, antimony and potassium tartrate intravenously, sulfonamides and iodides all have been tried without success.

Although the prognosis is almost hopeless, a few recoveries have been reported. Every effort should be made to support the general resistance of the patient by rest in bed and a good diet, supplemented by liver extract and all the known vitamins.

Martin and Smith have shown that cases of blastomycosis that have developed a marked sensitivity to the products of the fungus are resistant to therapy and may grow rapidly worse when treated with potassium iodide. If these patients are desensitized by gradually increasing doses of the *Blastomyces* vaccine, improvement can be accelerated by potassium iodide therapy. Since hypersensitivity to coccidioidin is such a striking feature in the early stages of progressive coccidioidomycosis, it would seem a logical procedure to desensitize the patient with coccidioidin, following the schedule and dosage outlined in the section on treatment of blastomycosis. Jacobson has recommended the use of a special extract of the organisms, prepared by mixing equal parts of the filtrate from a broth culture and the filtrate from the macerated organisms. Jacobson treated thirty patients over a period of 5 years by injecting the special extract described above, supplemented by intragluteal injections of 5 cc. of colloidal copper. Improvement was noted in a number of cases, and some cures were obtained.

X-RAY THERAPY may be used in the treatment of localized lesions. Amputation should be considered when the lesions are limited to an extremity and there is no clinical indication of involvement elsewhere.

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Geographic Distribution.—Most cases of this infection have been reported from Brazil, particularly in the São Paulo, Rio de Janeiro and Minas Gerais areas. The disease also has been reported from Argentina, Paraguay, Venezuela and Peru (Fig. 36.)

Source of Infection.—The origin of the infecting organism is not known, but the disease is contracted presumably from some exogenous source in nature.

Age, Sex, Nationality, and Occupation Incidence.—The following data are derived from de Almeida's review of 570 cases. The infection is most prevalent in young adults, the highest incidence occurring between the ages of 20 and 30. The great majority of the patients were males (498) as compared to females (52), giving a ratio of [illegible] most frequently in manual laborers, particularly those whose work is of such a nature that vegetative material is brought into direct contact with the skin

SYMPTOMATOLOGY

The most characteristic single clinical feature common to practically all cases of South American blastomycosis is the enlargement of lymph nodes. The clinical type of infection is determined largely by the site at which the fungus enters the body. De Almeida and other South American workers classify the infection under the following clinical headings: (1) a cutaneous form characterized by cutaneous and mucosal lesions, particularly in the region of the mouth and nose; (2) a lymphangitic type beginning as localized lymph node enlargement, most often in the neck, supraclavicular or axillary regions; (3) a visceral form with lesions of the liver, spleen, pancreas, intestines and other abdominal organs; and (4) a mixed type which involves skin and other organs to produce a varied clinical picture

Cutaneous Blastomycosis.—This form of the infection probably would be described better by the term "mucocutaneous" because the primary lesion is found most often on the mucosal surface of the tongue, palate, gums, cheeks, lips or nose. (Fig. 37.) Primary skin lesions usually occur on the skin around the mouth or nose.

When the infection begins on the MUCOSA, it appears as a small papule which soon ulcerates. The borders of the lesion are not elevated, and the surface characteristically shows one or more tiny yellow or reddish areas As the ulcers enlarge peripherally, the in-

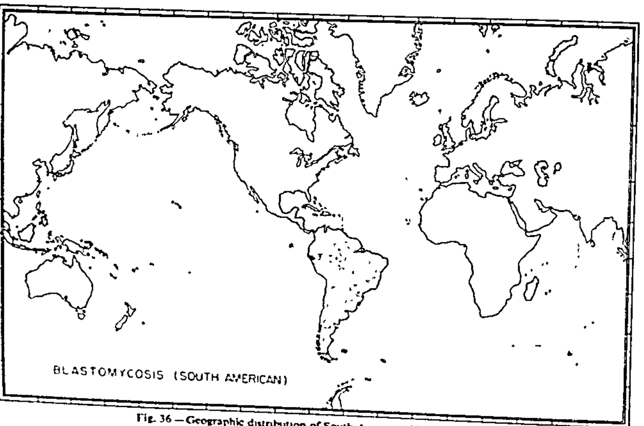


Fig. 36 — Geographic distribution of South American blastomycosis.



of the ly eous type. (After
-fedica," 1)



Fig 33 —South American blastomycosis Note the mucocutaneous ulceration bout the mouth (After Revista de Sanidad y Asistencia Social 5 Caracas, enezuela)

fection invades deeper into the subcutaneous tissues New lesions appear on the neighboring mucous membranes until there is extensive involvement which finally may lead to complete destruction of the epiglottis, vocal cords and uvula. The clinical appearances of these lesions are quite characteristic and usually can be recognized without difficulty by clinicians familiar with the disease

The REGIONAL LYMPH NODES become enlarged very early after the appearance of the initial lesion. As the mucosal lesions increase in size and number, the lymph nodes of the neck become larger, undergo massive necrosis and rupture through the skin, giving rise to perma- [illegible]

[illegible]

secondary dermal lesions.

The lesions are very painful and cause considerable difficulty in the ingestion of food. The patient gradually becomes weaker and dies in cachexia as a result of starvation and terminal pyogenic infection In fulminating cases, death may occur within 2 or 3 months after the initial infection; other patients may live for 2 or 3 years and, occasionally, longer.

When the infection gains entry through the SKIN, the first lesions are found in the deeper layers of the skin or in the more superficial parts of the subcutaneous tissue. The epidermis over the lesion becomes hyperkeratotic and at times even papillomatous. As the infection progresses, it extends deeper into the subcutaneous tissues. Necrosis occurs in the center of the lesion, leaving a deep crater surrounded by a hard hyperkeratotic wall. (Fig. 38.) These ulcer- [illegible]

[illegible]

this form of infection. (Fig. 39.) The organism presumably enters through the mucosa of the nasopharynx without producing a papule or ulcer at the site of entry. Often these enlarged lymph nodes may represent the only clinical manifestations of the disease for a period of several months. Eventually, the lymph nodes become necrotic and drain through the skin.

Visceral Blastomycosis.—That the portal of entry in this form of infection is the gastro-intestinal tract is suggested by postmortem studies which have shown that the most extensive lesions are to be found in the CECAL and APPENDICEAL REGIONS. The early symptoms



Fig 39.—South American blastomycosis of the lymphatic-visceral type, simulating Hodgkin's disease (After de Almeida, "Mycologia Medica," São Paulo, Brazil)

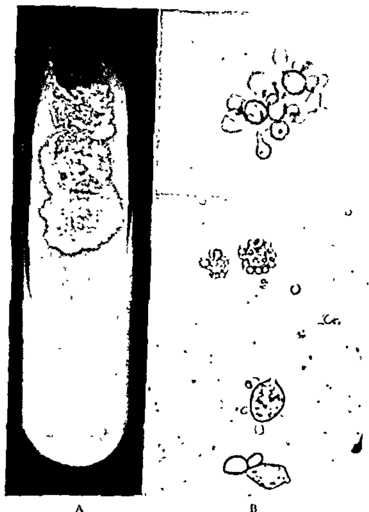


Fig 41.—*Blastomyces brasiliensis* A Yeastlike culture on beef infusion agar, twelve days, at 37° C. B Multiple budding forms from beef infusion glucose agar at 37° C. × 700.

from the microscope condenser. *B. brasiliensis* appears in such preparations as single and *multiple* budding, thick-walled, yeastlike cells, 10 to 60 μ in diameter. The single budding cells, 10 to 30 μ in diameter, are indistinguishable from those seen in Gilchrist's disease; and search should be made for the diagnostic multiple budding cells, which may be as large as 60 μ in diameter and characteristically show numerous buds which are often as small as 1 to 2 μ in diameter. Large buds, up to 10 μ in diameter, also may be found.

Cultures.—The infected materials (pus, curettings or biopsied nodes) should be cultured on blood agar plates at 37° C and on Sabouraud's glucose agar slants incubated at room temperature. All cultures should be held for at least 4 weeks before discarding as the fungus grows very slowly on primary isolation.

On blood agar, beef infusion glucose agar or Sabouraud's glucose agar at 37° C, the fungus grows slowly and develops smooth to cerebriform, yeastlike colonies. (Fig. 41 *A*.) Microscopically, the growth is composed of single and multiple budding, yeastlike cells, indistinguishable from the tissue forms seen in direct examination of material from lesions (Fig. 41 *B*.)

On Sabouraud's glucose agar at room temperature, the mycelial phase of the fungus develops as a SLOW GROWING, heaped, membranous or wrinkled colony with a short nap of white aerial mycelium which tends to become brown with age (Fig 42 *A*) Microscopically, a few sessile, oval to round conidia may be seen, not unlike those seen in cultures of *B. dermatitidis* maintained at room temperature (Fig. 42 *C*.) A few strains tend to remain glabrous, wrinkled to cerebriform, when maintained at room temperature (Fig 42 *B*) Both types of culture can be converted to the yeastlike phase by subculturing to fresh media and incubating at 37° C.

Animal Inoculation.—Infected material from the lesions should be inoculated intratesticularly into guinea pigs and intraperitoneally into mice Saline suspensions of pure cultures of the yeastlike phase grown at 37° C are pathogenic for these animals The infection develops slowly and it may require 5 to 6 weeks before visible lesions can be detected. Such lesions are seen as blastomycotic nodules scattered through the mesentery, on the spleen, liver and diaphragm, and direct microscopic examination of material from these areas shows the characteristic single and multiple budding tissue forms of the fungus

Mycologic Diagnosis.—Direct microscopic examination of material from the lesions should demonstrate the large, spherical,

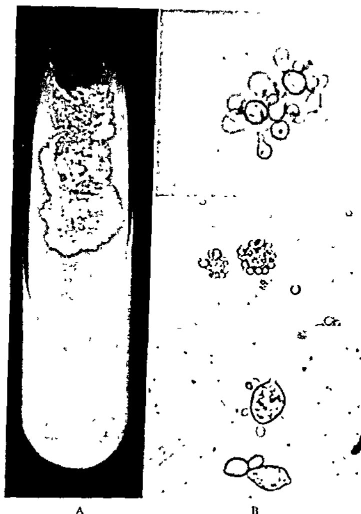


Fig. 41.—*Blastomyces brasiliensis*. *A*. Yeastlike culture on beef infusion agar, twelve days, at 37° C. *B*. Multiple budding forms from beef infusion glucose agar at 37° C. × 700

thick-walled single and multiple budding forms of the fungus. When cultured, the fungus develops as a yeastlike organism (tissue form) at 37° C. or as a filamentous moldlike organism at room temperature. This fungus is similar to *B. dermatitidis* in that the latter also produces yeastlike and moldlike cultures at 37° C. and room temperature respectively. *B. brasiliensis*, however, can be differentiated from *B.*

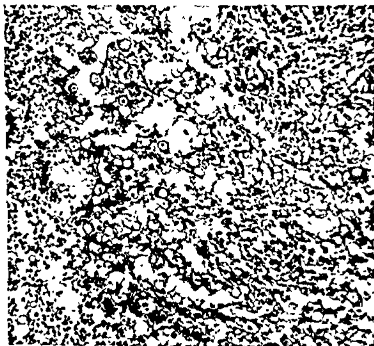


Fig. 43.—South American blastomycosis. Numerous rounded forms similar to common forms in North American blastomycosis and coccidioidomycosis. Polymorphonuclear cell reaction prominent. From lymph node. H & E. × 175.

dermatitidis by [illegible]
phase and by th[illegible]
a less extensive [illegible]
phase.

Blastomyces brasiliensis (Splendore) Conant and Howell, 1941. **Synonymy.**—*Zymonema brasiliense* Splendore, 1912, *Paracoc-*

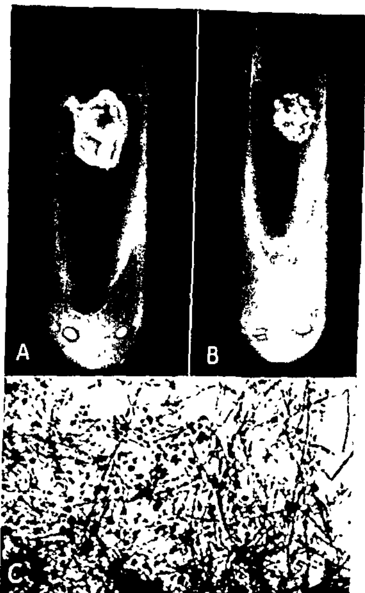


Fig. 42 —*Blastomyces brasiliensis* *A*. Filamentous type of culture *B* Smooth, glabrous type of culture Both *A*. and *B* on Sabouraud's glucose agar, three weeks, at room temperature *C*. Small, smooth-walled, round to pyriform conidia from filamentous culture on Sabouraud's glucose agar, three weeks, at room temperature. × 600.

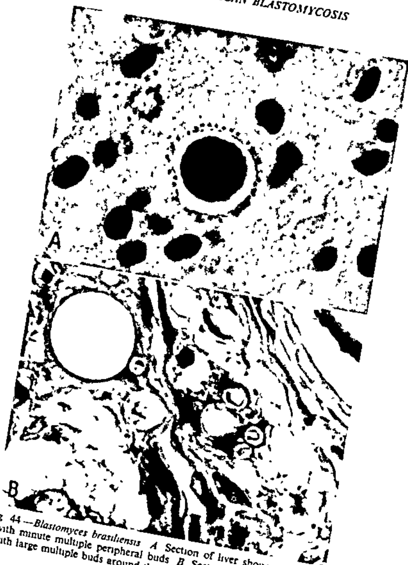


Fig 44 —*Blastomyces brasiliensis* *A* Section of liver showing large parent ell with minute multiple peripheral buds *B* Section of liver showing parent ell with large multiple buds around the periphery × 1300

cidioides brasiliensis Almeida, 1930; *Paracoccidioides cerebriformis* Moore, 1935; *Paracoccidioides tenuis* Moore, 1935.

PATHOLOGY

The gross and microscopic changes caused by *B. brasiliensis* are very similar to those produced by the invasion of tissue with the organisms of North American blastomycosis and coccidioidomycosis.

Biopsy.—In sections of infected tissue, the type of cellular reaction is essentially similar to that seen in North American blastomycosis with large numbers of giant cells, some containing organisms. In some areas, abscess formation with polymorphonuclear reaction is predominant. In other areas there are focal lesions with necrotic and caseous centers and a peripheral zone composed of giant cells, macrophages, lymphocytes, fibroblasts and collagen. (Fig. 43.)

Certain of the tissue forms of *B. brasiliensis* are indistinguishable from those of *B. dermatitidis*, and to make the diagnosis it is often necessary to examine the section carefully in order to find the characteristic pathognomonic stages of the fungus. For example, forms with minute dotlike projections from the periphery of the capsule (Fig. 44 *A*) occur frequently in giant cells. In addition, exceedingly small, dot-like forms sometimes are found free in the cytoplasm of giant cells. These minute forms are obviously buds pinched off from the parent cell. Forms with large peripheral buds also occur (Fig. 44 *B*). In other places, the shell of the organism, often crumpled or distorted, is all that can be seen.

In some areas, enormous numbers of the organisms lie free in the tissues or interspersed with forms occurring within giant cells. Necrosis in such areas is common.

Autopsy.—Postmortem examinations have shown extensive intestinal lesions, consisting of ulcers which apparently start in the lymphoid tissue and then extend beyond the confines of such tissue. [illegible] spleen, liver [illegible] skeleton [illegible]

IMMUNOLOGY

Serology.—Complement fixing antibodies can be demonstrated in the sera of patients with South American blastomycosis, but no data are available concerning the use of a standard serologic method for antibody determination in a large series of cases. Fonseca, for example, used filtrates of old broth cultures as antigenic materials, and found that these substances produced non-specific reactions in

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Chapter V

GEOTRICHOSIS

ALTHOUGH ONLY a few instances of geotrichosis have been described, a discussion of the disease is given here because the infection may be confused with North American blastomycosis, especially if the diagnosis is made by the appearance of the organisms on direct smear and cultural studies are not done.

Definition.—Geotrichosis is an infection due to one or more species of *Geotrichum*, a fungus capable of producing lesions in the mouth, intestinal tract, bronchi and lungs

Source of Infection.—It is likely that the infection, like moniliasis, is endogenous in origin since the fungus frequently can be found in the mouths and intestinal tracts of normal individuals In a series of 314 stool specimens obtained from medical students, nurses and patients without gastro-intestinal symptoms, Schnoor cultured

that positive results also were obtained in patients with chromoblastomycosis, sporotrichosis and epidermophytosis.

Hypersensitivity.—The intracutaneous injection of antigens prepared from cultures have been reported to produce focal reactions with redness, pain and burning, and some patients react with generalized symptoms such as malaise and fever.

DIFFERENTIAL DIAGNOSIS

The cutaneous lesions of South American blastomycosis must be differentiated from those of cutaneous leishmaniasis, yaws, syphilis, tuberculosis and certain neoplasms. Such lesions may simulate, also, other mycoses such as histoplasmosis, coccidioidomycosis, actinomycosis, North American blastomycosis, cryptococcosis and sporotrichosis.

The lymphangitic and visceral types may be confused with visceral leishmaniasis, tuberculous adenitis, tuberculous peritonitis, syphilis, [illegible] *produced by abdominal actinomycosis before the development of* sinuses.

PROGNOSIS

The disease usually is fatal. Some cases have been reported as cured, but Fonseca has expressed the opinion that the diagnosis in such patients may be questioned.

TREATMENT

De Almeida reports that iodides sometimes cause improvement in early cases, but that use of this drug may accelerate the spread of infection when the patient is already in an advanced stage of the disease. The harmful effect of iodides in the hypersensitive patient with North American blastomycosis has been discussed elsewhere (p. 47). Since patients with South American blastomycosis also may show hypersensitivity to the invading fungus, it is suggested that preliminary skin tests be performed and that desensitization of hypersensitive patients be attempted before iodide administration. Under such circumstances, iodides should be administered by the schedule outlined for the treatment of North American blastomycosis (p 48).

Unconfirmed reports have reached us that South American blastomycosis responds to treatment with sulfapyridine.

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Chapter V

GEOTRICHOSIS

ALTHOUGH ONLY a few instances of geotrich[illegible] [illegible] appearance of the organisms on direct smear and cultural studies are not done

Definition.—Geotrichosis is an infection due to one or more species of *Geotrichum*, a fungus capable of producing lesions in the [illegible] patients without gastro-intestinal symptoms, [illegible] nurses [illegible] Schnoor cultured

Geotrichum in 29 per cent of the samples. Since there has been no careful study of saprophytic and pathogenic strains comparable to those of Benham on *Monilia* and *Cryptococci*, it is a waste of time to name new species or rename species from a study of the descriptions in the literature.

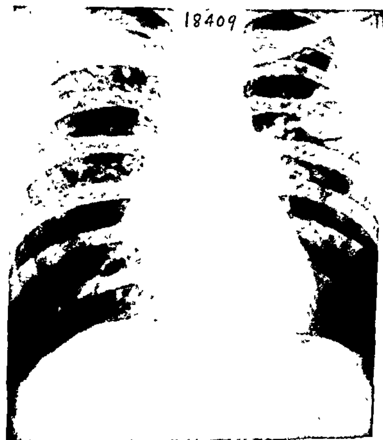


Fig. 45 —Geotrichosis of the lungs There are two cavities in the right upper lobe and a larger one in the left upper lobe The lesions disappeared with potassium iodide therapy

Age, Sex, Race, and Occupation Incidence.—Since only limited data are available, no conclusions can be drawn concerning any age, sex, race or occupational predisposition to the disease

SYMPTOMATOLOGY

Oral, intestinal, bronchial and pulmonary forms of the disease have been described.

ORAL GEOTRICHOSIS is characterized by white patches in the mouth which are indistinguishable clinically from thrush It can be differentiated only by direct examination of material from the lesions, in which the characteristic rectangular spores are found.

There is some doubt as to whether INTESTINAL GEOTRICHOSIS is a primary disease or not since the organisms are found frequently in normal individuals. An occasional patient has been observed to have blood in the stools and symptoms of colitis, associated with large numbers of *Geotrichum* spores in the bloody pus found in the feces, and the number of organisms has been found to decrease as the patient improves clinically.

BRONCHIAL GEOTRICHOSIS is the most frequently recognized manifestation of the infection The patient's symptoms are those of a chronic type of bacterial bronchitis with persistent cough and expectoration of a peculiar mucoid or gelatinous type of sputum, which occasionally is blood streaked. Numerous medium and coarse rales are heard, particularly at the bases. There is little, if any, elevation of the temperature or pulse. Except for the harassing effects of chronic coughing, the general health of the patient is not affected seriously.

PULMONARY GEOTRICHOSIS simulates tuberculosis, with an elevation of temperature, pulse and respiration and leukocytosis The sputum is mucopurulent but light in color, in contrast to the greenish, mucopurulent sputum of tuberculosis Frank hemoptyses are not rare In one of the cases reported from this clinic, there were bilateral cavities in the upper third of both lung fields. (Fig 45.) On physical examination there may be dulness, altered breath sounds with fine and medium rales, the picture resembling that found in acute reinfecti tuberculosis. The organisms are present in abundance in the purulent or bloody sputum and can be cultured without difficulty on Sabouraud's medium

X-rays.—Chest films of patients with the BRONCHIAL FORM of geotrichosis show a diffuse peribronchial thickening which is accompanied sometimes by a fine mottling in the mid-lung fields or in the bases of the lungs

The PULMONARY FORM shows smooth, dense patches of infiltration with or without the presence of thin-walled cavities The lesions may be located in any part of the lungs, but may be confined to the upper lobes (Fig. 45)

MYCOLOGY

Species of *Geotrichum* are isolated frequently from the sputum, skin and feces of patients without clinical disease, and a diagnosis of geotrichosis, like that of moniliasis, is justified only by repeated demonstrations of the fungus by direct smears and the exclusion of other possible etiologic agents.

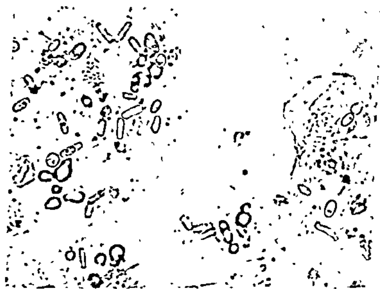


Fig 46.—*Geotrichum sp* · Rectangular, rounded-end forms, arthrospores in sputum. × 375

Direct Examination.—Sputum or pus should be examined by placing a loopful on a slide and pressing to a thin film under a cover glass Ten per cent potassium hydroxide may be added to the preparation for clearing if necessary Direct examination of purulent or bloody bits of feces also will reveal the organisms The fungus appears in fresh preparations as oblong or rectangular cells, 4 by 8 μ, with somewhat rounded ends, or as large, spherical cells, 4 to 10 μ in diameter (Fig 46.)

Cultures.—Infected material, such as sputum, pus or feces, should e streaked on Sabouraud's glucose agar plates since we have found hat colonies of *Geotrichum* are obtained more frequently when lates rather than slants are used The cultures should be maintained t room and incubator temperatures for at least 2 weeks.

At 37° C., most of the growth occurs just below the surface of the agar, the surface colonies showing only a central small colony growth. urrounding the central portion is a marked, wide zone of mycelium rowing down into the agar. At room temperature, the fungus grows [illegible]

ize and roundness of their ends. (Fig. 47 *B.*) Also, there are seen nany spherical cells, 4 to 12 μ in diameter, which are segmented rom the hyphae but fail to remain rectangular. The rectangular ells usually germinate by a germ tube from one corner, a very haracteristic finding in cultures of *Geotrichum* At first, the spherical [illegible]

ultures are obtained which remain soft and form arthrospores by egmentation of the hyphae.

The spherical, somewhat thick-walled cells found in clinical naterial should not be mistaken for the budding forms of *Blastonyces dermatitidis.* The preparation should be examined carefully or the presence also of the rectangular cells which never are found n North American blastomycosis. Cultures of *B. dermatitidis,* when he fungus is first isolated, often show segmentation of the hyphae nto oblong *Geotrichum*-like arthrospores, but these cultures evenually become filamentous (moldlike) and produce conidia, in conrast to *Geotrichum* which remains soft and yeastlike and continues o produce arthrospores by segmentation

DIFFERENTIAL DIAGNOSIS

The disease may be suspected from the presence of the peculiar nucoid, gelatinous sputum, but the diagnosis cannot be established without the demonstration of the organism both by direct examination and by culture. The direct examination is essential because occasional colonies of *Geotrichum* may be found in cultures of oral secretions from normal individuals

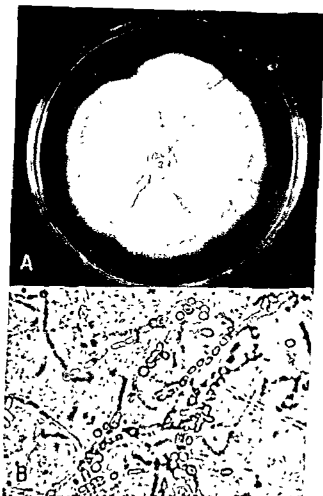


Fig. 47—*Geotrichum sp* *A* Colony on Sabouraud's glucose agar, nineteen ays, at room temperature. *B* Mycelium segmenting to form arthrospores, from

For some unknown reason, *Geotrichum* not infrequently is found in the sputum in association with Friedländer's bacillus, and it is often impossible to determine which organism is the primary invader. We have studied one patient with a chronic non-tuberculous infection of the lungs of 20 years' duration who has had in his sputum for over 5 years both Friedländer's bacillus and a species of *Geotrichum*.

Geotrichum may be a secondary invader in pulmonary tuberculosis In one patient with a mottled disease of the right upper lobe, *Geotrichum* was present in abundance in the sputum by direct examination and culture, and no tubercle bacilli could be demonstrated even by guinea pig inoculation. Treatment with potassium iodide eliminated the cough and expectoration, but 6 months later her symptoms returned and tubercle bacilli without *Geotrichum* were found in the sputum.

Geotrichosis must be differentiated from tuberculosis, bacterial infection of the lungs and certain of the mycotic infections, particularly moniliasis, blastomycosis, cryptococcosis and coccidioidomycosis.

PROGNOSIS

The prognosis usually is good with treatment One of the chief reasons for recognizing this infection as a specific entity is to avoid confusing geotrichosis with North American blastomycosis, in which the prognosis is poor

TREATMENT

Oral infections respond to local treatment with gentian violet, as described for the treatment of oral thrush caused by *Candida albicans*. (Page 148.)

The intestinal form should be treated by gentian violet in salol-coated capsules in doses of 32 mg 3 times a day since laboratory tests show that this drug in a dilution of 1 1,000,000 will inhibit the growth of *Geotrichum* in broth cultures.

The bronchial form of the disease responds readily to treatment with potassium iodide given by the rapid method described for the treatment of blastomycosis (p. 48)

The pulmonary form of the disease should be treated by the same regimen employed for tuberculosis, including rest in bed and a high vitamin diet. A thorough study for the presence of tubercle bacilli, including guinea pig inoculation, should be made before

iodides are administered. An autogenous vaccine should be tried if the patient does not respond to treatment with iodides.

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Chapter VI

CHROMOBLASTOMYCOSIS

(Chromomycosis, Verrucous Dermatitis)

THE NAME "chromoblastomycosis" is misleading because the organism does not form buds (blastospores) in tissue or in culture. The organism has a brownish color when seen unstained in the tissues, but this does not warrant the name chromomycosis which implies that the lesions have a characteristic color. The term "chromoblastomycosis" has been retained because it has become established so firmly in the literature

Definition.—Chromoblastomycosis, or verrucous dermatitis, caused by *Hormodendrum Pedrosoi, Hormodendrum compactum* or *Phialophora verrucosa*, is characterized by the formation of warty cutaneous nodules which develop very slowly, ultimately forming prominent papillomatous vegetations which may or may not ulcerate. Usually, the lesions are confined to the feet and legs but have occurred on the hands, face, ear, neck, chest, shoulders and buttocks With few exceptions, the lesions have been confined to the head and extremities.

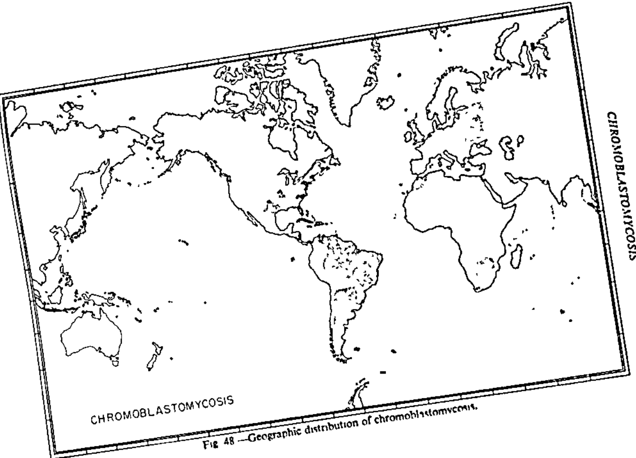


Fig 48 —Geographic distribution of chromoblastomycosis.

Geographic Distribution.—The disease has been reported from various parts of the world. It is known to occur in North America, Cuba, Puerto Rico, Santo Domingo, Guatemala, Costa Rica, Brazil, Venezuela, Argentina, Paraguay, Uruguay, Russia, South Africa, Algeria, Japan, Java and Sumatra. (Fig. 48)

Source of Infection.—There is no evidence of direct transmission from man to man. In their review of 102 cases, Weidman and Rosenthal were impressed with the large number of cases in which the lesions developed following an injury by some form of wood, whether living or dead. This view is supported by the recent work of Conant and Martin who have found that certain strains of *Phialophora* isolated from wood pulp by Kress and his co-workers were identical morphologically and serologically with strains of *Phialophora verrucosa* isolated from patients.

Age, Sex, Race, and Occupation Incidence.—More than one-half of the cases have occurred in patients between the ages of 30 and 50 years. Males apparently are more often affected than females. In their review of 102 cases of the disease, Weidman and Rosenthal report that the infection occurred in only three females. All races seem to be susceptible to infection. It has been observed in Japanese and Negroes, but most cases have been described as occurring in Caucasians of North America, Central and South America and Europe. The laboring classes are affected almost exclusively. One exception was Tschernjawski's patient, a literary worker who developed her disease subsequent to skin injuries following an accidental fall while riding horseback in the country.

SYMPTOMATOLOGY

The infection is located almost invariably on some exposed part of the body and nearly always is unilateral. An occasional case has been reported where both a leg and an arm were affected The lesion begins as a small, itchy papule which extends eccentrically and simulates a patch of ringworm. (Fig. 49.) The original patches are usually sharply limited, dull red or violaceous in color and present marked degrees of infiltration. After various intervals of time, often months later, crops of new lesions appear along the paths of lymphatic drainage The involved areas extend 1 to 2 mm. above the surrounding skin and frequently develop markedly elevated, hard, dull red or grayish nodules in the center, giving to the lesion a cauliflower-like appearance Some lesions become pedunculated, others become secondarily infected and ulcerate, but, in general, the

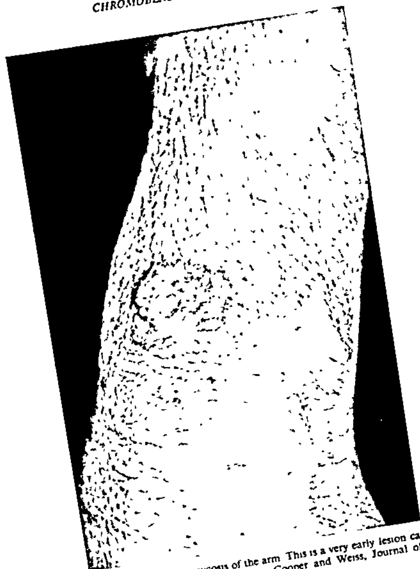
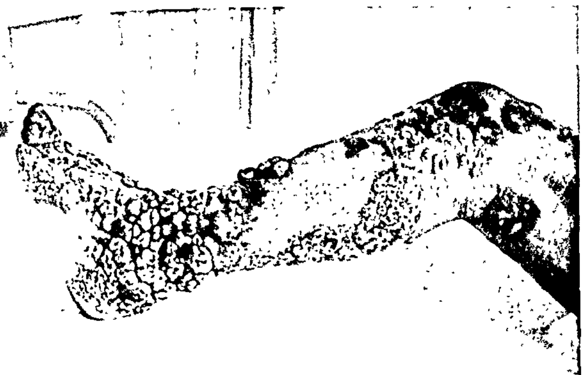


Fig. 49 —Chromoblastomycosis of the arm This is a very early lesion caused by *Phialophora verrucosa* (After Moore, Cooper and Weiss, Journal of the American Medical Association 122)



Chromoblastomycosis of the leg caused by *Hormodendrum Pedrosoi*. Note the cauliflower like ... the edema of the leg. (After Carrión and Koppisch, Puerto Rico Journal of Public Health and ... Medicine 9.)

ruption has a rather dry appearance. The infection progresses so lowly that it may take 4 to 15 years to involve an entire arm or leg. (Fig. 50.) Extensive fibrosis develops in the deeper tissues and the lymphatics become blocked, producing an elephantiasis of the extremity. The lesions are painless unless they are complicated by secondary bacterial infection. Some investigators state that itching is uncommon, but Carrión reports that his patients in Puerto Rico complained of severe pruritus Some lesions heal spontaneously,

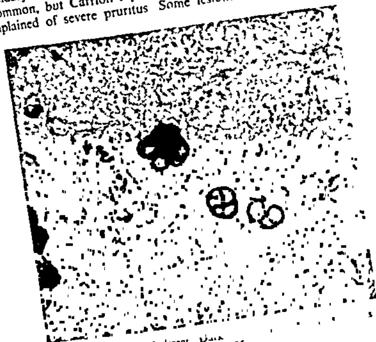


Fig 51.—*Hormodendrum Pedrosoi* Dark s from lesion. × 825

leaving only areas of hyperpigmentation. The infection rarely metastasizes although Carrión reported a patient with a primary lesion on the leg who developed a subcutaneous nodule in the opposite thigh and in the left forearm, and Montpellier and Catanei described a case in which metastasis to the quadriceps muscle occurred The general health of the patient, as a rule, remains good

As in tuberculosis and syphilis, the early lesions of chromoblastomycosis are so protean that the diagnoses can be made only by laboratory methods. (Fig 51) The cases studied by Weidman and

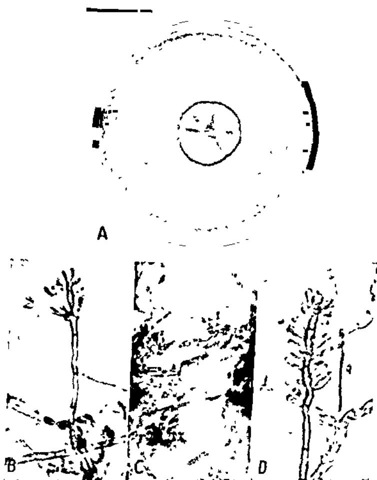


Fig. 52.—*A Hormodendrum Pedrosoi* Forty-one-day growth on Sabouraud's glucose agar at room temperature. *B Hormodendrum-type* of conidiophore × 800 *C Phialophora-type* of conidiophore × 400 *D Acrotheca type* of conidiophore. × 800

Rosenthal and by Moore, Cooper and Weiss were diagnosed by biopsy and culture before the typical nodules or verrucosities had appeared.

X-rays.—The disease apparently is confined to the cutaneous and subcutaneous tissues. There have been no reports of bone involvement

Laboratory Examination.—There is neither leukocytosis nor anemia unless secondary infection occurs.

MYCOLOGY

Hormodendrum Pedrosoi, *Hormodendrum compactum* and *Phialophora verrucosa* are the three recognized etiologic agents of chromoblastomycosis. Several new genera, which we think are unwarranted, have been created for the single species *H Pearosoi* because of the great variations displayed in its microscopic morphology in culture. Depending upon the medium used and the particular strain studied, organisms of this species vary in their method of spore production By placing undue emphasis on the predominant type of conidial formation in the particular strain being examined, this fungus has been placed in the genera. *Acrotheca*, *Trichosporium*, *Gomphinaria*, *Botrytoides*, *Hormodendroides*, *Phialoconidiophora* and *Fonsecaea*.

There is a valid objection, however, to the use of the generic name *Hormodendrum* since it is clearly a synonym of a previously described genus, *Cladosporium*. At this time, however, less confusion will be caused if the genus *Hormodendrum* is retained until general agreement is reaohed concerning a more suitable generic name for this pathogenic fungus.

Direct Examination.—Crusts from the verrucous lesions should be placed on a slide in a drop of 10 per cent potassium hydroxide and examined under a cover glass. The preparation may be heated gently over a low flame of a bunsen burner or alcohol lamp to hasten clearing Exudates from the lesions may be pressed to a thin film under a cover glass and examined directly.

The three fungi produce identical forms in tissue, so that the genus or species of fungus producing the infection cannot be determined by direct examination The organisms appear as single or clustered, round, thick-walled, dark brown bodies which multiply by splitting and *not by budding*. (Fig 51)

Cultures.—Material from the lesions should be cultured on Sabouraud's glucose agar at room temperature and held for at least 3 weeks before discarding Cultures of *Hormodenarum Pearosoi* and

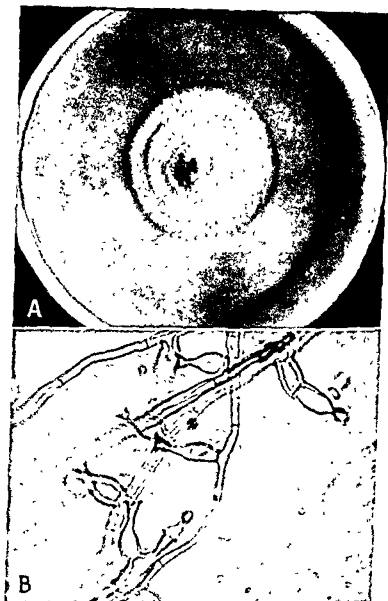


Fig 53 —*A* *Phialophora verrucosa* Twenty-eight-day growth on Sabouraud's glucose agar at room temperature *B* Conidiophores of *P. verrucosa* × 1500

Phialophora verrucosa produce slow growing colonies which are dark brown to black in color, with individual strains showing great variations in color, rate of growth and gross colony characteristics. (Fig 52, 53) *H. compactum* develops as a slow growing, heaped, brittle colony which is olive black in color. (Fig 54.)

Microscopically, *P. verrucosa* produces conidia from cups at the tip of flask-shaped conidiophores borne terminally or laterally, singly or in groups, on the aerial mycelium The conidiophores are about 3 to 4 μ wide and 4 to 7 μ long The conidia are thin-walled, oval cells, averaging 1.5 μ in width and 4 μ in length. In undisturbed preparations such conidia are held in compact masses at the cup-shaped tips of the conidiophores. This fungus differs from *H. Pedrosoi* and *H. compactum* in that the conidia develop exclusively from flask-shaped conidiophores. (Fig 53)

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varying lengths bearing conidia in branching chain formation Such conidia are single celled, vary from 3 to 6 μ in length and 1.5 to 3 μ in width and are connected in the chain by thick disjunctors When conidial chains are broken and the spores lie free in the preparation, they may be identified by their olive to brown color and the black points on the ends where they had been joined together (Fig 52 *B*) The *Acrotheca*-TYPE of sporulation is characterized by a conidiophore which develops as a terminal cell or as single lateral branches on the aerial hyphae. Such cells become swollen, assuming the shape of knotted clubs from which the conidia are borne on short protuberances along the length of the conidiophore. (Fig 52 *D*) The *Phialophora*-TYPE is characterized by flask-shaped conidiophores with a terminal cup-like structure bearing groups of conidia. (Fig 52 *C*.) The three types of conidial formation mentioned above can be found in all strains of *H. Pedrosoi* isolated from lesions of chromoblastomycosis; however, there is great variation among strains as to the most prominent type of sporulation If these differences are considered to be within the limits of specific variations, the single species *H. Pedrosoi* can be used to designate all of these varieties.

Only one strain of *H. compactum* has been isolated from chromoblastomycosis; the fungus grows very slowly on Sabouraud's glucose agar, producing a heaped, brittle colony which is olive black in color. Microscopically, this fungus is characterized by the formation of

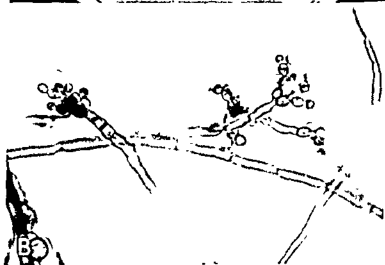


Fig 54 —*A Hormodendrum compactum* Forty-one-day growth on Sabouraud's glucose agar at room temperature *B*. Conidiophores of *H compactum* × 816.

terminal and lateral conidiophores bearing COMPACT MASSES of long, branching chains of subspherical conidia 1.5 to 2 μ by 2 to 3 μ in size. The *Phialophora*-TYPE of conidiophore is produced also in this species when grown on corn meal agar. This species differs from *H. Pedrosoi* by the compact arrangement of the conidial chains which are not easily dissociated and by the subspherical conidia. (Fig 54 *B*)

Animal Inoculation.—Laboratory animals do not develop chronic verrucous or papillomatous lesions when injected intracutaneously or subcutaneously with saline suspensions of cultures of the three fungi described above. Subcutaneous injections of such materials result in the formation of abscesses which rupture spontaneously and heal.

Mycologic Diagnosis.—Direct examination of crusts and exudate in 10 per cent potassium hydroxide preparations should reveal the characteristic spherical, dark brown, thick-walled, splitting cells which are pathognomonic for chromoblastomycosis. The dark brown to black, moldlike cultures obtained on Sabouraud's glucose agar at room temperature distinguish this group of fungi from other fungi pathogenic for man

Phialophora verrucosa Thaxter, 1915. Synonymy.—*Cadophora americana* Nannfeldt, 1927; *Phialophora macrospora* Moore and Almeida, 1936.

Hormodendrum Pedrosoi Brumpt, 1922. Synonymy.—*Acrotheca Pedrosoi* da Fonseca and Leao, 1923, *Hormodendrum algeriensis* Montpellier and Catanei, 1927; *Trichosporium Pedrosianum* Ota, 1928; *Trichosporium Pedrosoi* Langeron, 1929, *Hormodendron rossicum* Merin, 1930, *Gomphinaria Pedrosoi* Dodge, 1935, *Botrytoides monophora* Moore and Almeida, 1936; *Hormodendroides Pedrosoi* Moore and Almeida, 1936; *Phialoconidiophora Guggenheimia* Moore and Almeida, 1936; *Fonsecaea Pedrosoi* Negroni, 1936, *Hormodendrum japonicum* Takahashi, 1937.

Hormodendrum compactum Carrión, 1935 Synonymy.—*Phialoconidiophora compactum* Moore and Almeida, 1936

PATHOLOGY

Chromoblastomycosis is confined, as a rule, to the surface of the body. Hematogenous spread has been reported but twice, and it is not settled as to whether the regional lymph nodes become infected The diagnosis of the condition frequently is made by the examination of material obtained by biopsy

Biopsy.—Grossly, the lesions may be warty and hyperkeratotic,



Fig 55 —*Hormodendrum Pedrosoi* *A* Lesion in dermis Note giant cells containing clusters of the brown, septate bodies *B* Giant cells containing the round, septate, brown cells. × 750

but in some instances hyperkeratosis is absent. Microscopically, the presence of the organisms constitutes the prominent feature. (Fig. 55 *A*.) The fungi are found usually in the dermis, but sometimes are in the hyperplastic epidermal layer where they can be seen in either minute abscesses or giant cells. (Fig. 55 *B*.) The organisms are brown, grouped in clusters and provided with septae. In sections stained by Giemsa's method, the fungi assume a brownish-green tint. The minute abscesses show polymorphonuclear neutrophils immediately about the organisms; the intervening fibrous tissue contains macrophages, lymphocytes, eosinophils and plasma cells. Fibrous thickening of the dermis and of the subcutaneous tissue is prominent.

IMMUNOLOGY

Serology.—Complement fixing antibodies have been demonstrated in the sera of patients with chromoblastomycosis, but the procedure has little practical significance because the infectious process is superficial and the fungi can be demonstrated readily. However, by using the technic described in the appendix (p. 321), we were able to demonstrate: (1) that the serum of the North Carolina patient, infected with *H. Pedrosoi*, fixed complement with strains of *H. Pedrosoi* isolated from patients in South America and Puerto Rico; (2) that there was cross fixation with strains of *Phialophora verrucosa;* and (3) that there was no fixation with other pathogenic fungi, such as *Blastomyces dermatitidis* and *Sporotrichum Schenckii*, or with a series of non-pathogenic pigment-producing fungi, including plate contaminants of the genus *Hormodendrum*.

As in North American blastomycosis, it was noted that the antibody titer in our patient could be correlated with the severity of the disease, the titer dropping as clinical improvement was noted. Antibodies may be produced in rabbits by subcutaneous injections of living fungi, and it was by this method that we were able to demonstrate the antigenic similarity between strains of pathogenic *P. verrucosa* and a strain of *Cadophora americana* isolated from wood pulp but morphologically indistinguishable from *P. verrucosa*.

Hypersensitivity.—There are few data concerning the role of hypersensitivity in the pathogenesis of the infection. Our patient did not react to the intracutaneous injections of a heat-killed autogenous vaccine. However, it has been reported that rubbing a live culture on the skin of an infected patient resulted in the formation of a pustule which lasted 2 weeks, and intracutaneous injection of the live culture produced a progressive nodule.

DIFFERENTIAL DIAGNOSIS

The early lesions must be differentiated from various coccal infections, tuberculosis verrucosa cutis, syphilis, yaws, leishmaniasis, *moniliasis, blastomycosis, sporotrichosis* and *rhinosporidiosis* The disease has been confused with lupus erythematosus, lupus vulgaris and leprosy. In patients with elephantiasis, the infection should be differentiated from maduromycosis.

PROGNOSIS

Chromoblastomycosis is not fatal, but complete cure is rare in patients in whom the disease is far advanced before treatment is *instituted.*

TREATMENT

When the infection is diagnosed in its incipient stage, an attempt should be made to destroy the lesions by surgical excision or electrocoagulation. Iodide therapy should be used as supplementary treatment. Carrión excised some of the larger lesions presented in several of his patients; open ulcers developed at the site of the excisions, but these healed eventually under routine treatment.

Sodium iodide by intravenous injection produced definite improvement in the case reported by Carrión and Koppisch who began treatment with 1 Gm. daily and gradually increased the dose to 9 Gm. daily near the end of the second year of treatment. Under this intensive treatment the nodules did not disappear completely, and a biopsy of the skin showed no essential change in the pathologic picture; the typical fungus cells were present microscopically and were cultured from the biopsy specimen.

Iontophoresis with copper sulfate was employed with success in the patient reported by Martin, Baker and Conant. The normal areas of skin were covered with petroleum jelly, and the hand and forearm were immersed in a bath containing a 1 per cent solution of copper sulfate The negative electrode was placed on the upper arm and the positive in the solution, and a galvanic current of 2 5 ma. was passed through the bath for 30 minutes. The treatment was given daily, and after 9 weeks the current was increased to 10 ma. The cauliflower-like growth became heavily stained with copper sulfate and the symptoms of itching and burning disappeared gradually. There was a gradual reduction in the height of the nodules during the 5 months of treatment and the skin overlying the warty growths became smooth and glossy There was little change in the lym-

phedema, but the hand became more flexible and there was great functional improvement. A biopsy at the end of the treatment period showed atrophic epidermis over the residual nodule and there was marked scarring of the dermis with lymphocytic perivascular infiltration. An occasional giant cell and pseudotubercle were present still, and one giant cell was found which contained several brown organisms. However, no organisms could be demonstrated in the area just beneath the epidermis although originally the fungi were found most abundantly in this part of the skin

In our opinion, amputation should not be done since the lesions rarely become infected secondarily and the disease does not become generalized The spread of infection usually can be controlled by medical treatment, and the infected limb restored to partial usefulness.

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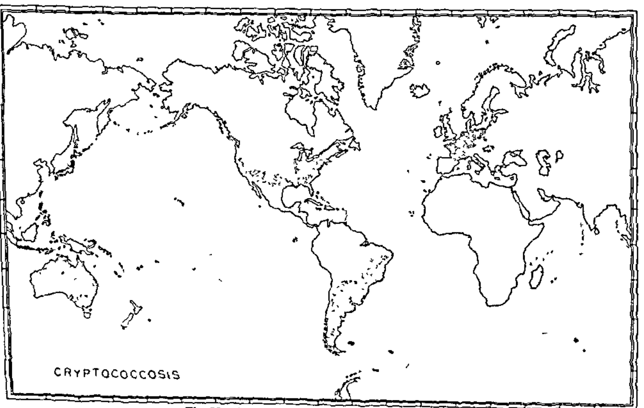


Fig. 56.—Geographic distribution of cryptococcosis.

Chapter VII

CRYPTOCOCCOSIS

(European Blastomycosis, Torulosis, Busse-Buschke's Disease)

THIS INFECTION is a true "blastomycosis" in that the fungus appears in tissue as a budding fungus. The term "European blastomycosis," introduced to distinguish cryptococcosis from North American blastomycosis or Gilchrist's disease, is inappropriate because the infection is not limited to Europe but occurs in many parts of the world.

Definition.—Cryptococcosis is a subacute or chronic infection, caused by *Cryptococcus neoformans* (*Torula histolytica*), which may involve the lungs, skin or other parts of the body but has a marked predilection for the brain and meninges

Geographic Distribution.—*C. neoformans* infections have been reported from Germany, France and Italy and, in the Southwestern Pacific region, from Australia, Japan, the Philippines and some of the islands in the Dutch East Indies. In South America, cases have been reported from Brazil, Argentina and Paraguay. In the United States, most cases have been reported from the eastern part of the country and in a zone extending across the southern states from Florida to California. (Fig 56.)

Source of Infection.—Cryptococcosis is not transmitted from man to man. Naturally occurring infections have been observed in animals, but there is no evidence that man has ever contracted the disease from an infected animal. Cryptococci pathogenic for animals have been isolated from fermenting fruit juices, but, again, there is no record of any human contracting the disease from such a source

Benham isolated a number of cryptococci from the skin of normal individuals and compared them with strains isolated from cryptococcosis and from various exogenous sources in nature. The non-human strains differed culturally, morphologically and serologically from those of h[illegible] but some of the non-pathogen[illegible] skin

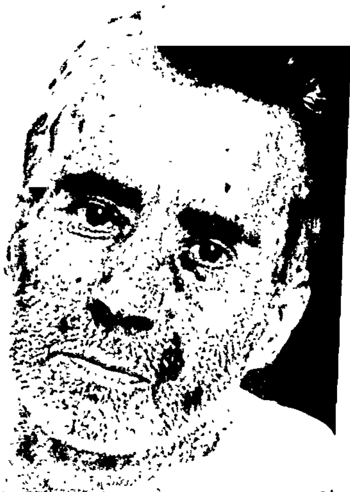


Fig. 57.—Cryptococcosis of the skin. Note the acneform lesions and open ulcers. (After Flavio L. Niño, Universidad de Buenos Aires, Imprenta de la Universidad, Monografia No. 3)

ated only by their reduced pathogenicity for animals. These observations suggest that cryptococcosis may be derived from an endogenous source.

Age, Sex, and Race Incidence.—Cryptococcosis has been reported in children less than 10 years of age and in adults more than 70, but most of the cases have occurred between the ages of 40 and 60 years. The ratio of males to females is less than 2 to 1. In a series of sixty cases of *Cryptococcus* infection of the central nervous system, thirty-nine patients were males and twenty were females. All races are apparently equally susceptible.

SYMPTOMATOLOGY

It is thought that the fungus enters the body, as a rule, through the respiratory tract. Such a viewpoint is supported by the observations that cases of primary pulmonary cryptococcosis are not rare and that a history of a mild but definite respiratory infection usually can be obtained from patients suffering from the most common form of the disease, *Cryptococcus* meningitis. However, the organism may enter the body through the skin or nasopharyngeal mucosa and occasionally through the intestinal tract Isolated lesions have been reported in the skin and subcutaneous tissues (Fig 57), lymph nodes, tongue, knee, muscles of the back and pelvis; these lesions may remain localized, but frequently they spread to the brain and meninges Levin, in reviewing forty-seven cases from the literature, found that the central nervous system was involved in thirty patients, lung infection occurred in only nine patients, and the remaining eight patients had generalized infections.

Pulmonary Cryptococcosis.—The symptoms of primary pulmonary infection are not diagnostic. The patient presents the picture of a subacute infection with low grade fever and mild cough. Some patients raise no sputum, others expectorate a small amount of mucoid sputum which is rarely blood streaked. The pulmonary lesions may develop in any part of the lungs They are frequently bilateral, but may be unilateral and confined to one upper lobe. (Fig 58) Dulness and altered breath sounds are found commonly, but rales are inconstant except in patients in whom there is a terminal miliary dissemination to the lungs.

Central Nervous System Cryptococcosis.—Symptoms in this form of infection usually appear gradually, beginning with intermittent frontal headache which later becomes more severe and continuous Occasionally, the onset is sudden with violent and excruciating head-

ache and vomiting. Dizziness, vertigo, stiffness and pain in the back of the neck are common symptoms. As the disease progresses, evidence of severe mental disturbances appears with depression, disorientation, apathy, restlessness, irritability and delirium.

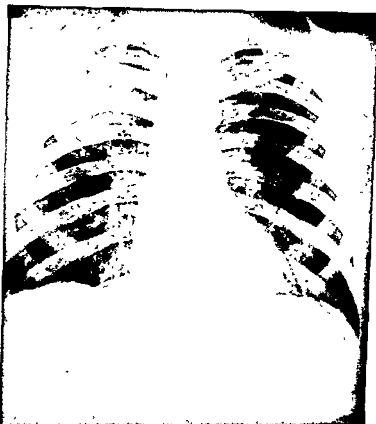


Fig 58.—Cryptococcosis of the lungs The lesion was confined to the right upper lobe The patient died after an extension to the brain.

The physical signs of central nervous system infection are those of any chronic meningitis, namely, stiffness of the neck with positive Kernig and Brudzinski signs. Amblyopia is common and strabismus, nystagmus, ptosis, diplopia, ataxia and hemiplegia are noted occasionally. Neuroretinitis and papilloedema are observed frequently.

In spite of the severity of symptoms related to the central nervous system, the patient usually does not present the picture of an acute

infection. The blood pressure remains normal, the temperature rarely rises above 101° F. and the pulse rate is seldom over 100 per minute. As the disease progresses, there is marked loss of weight and strength, and the patient ultimately becomes comatose and dies of respiratory failure



Fig 59—Cryptococcosis of the lungs The lesions disappeared after prolonged treatment with sulfadiazine (Courtesy of Dr. E E Menefee)

X-rays.—In primary pulmonary infections the shadows are often dense and massive, resembling a massive tuberculous lesion or neoplasm (Fig 59) Cavity formation is unusual The mediastinum

rarely is involved, a valuable point in differentiating cryptococcosis from the pulmonary lesions of actinomycosis, North American blastomycosis and coccidioidomycosis. Miliary lesions may be present throughout the lungs following a terminal dissemination of the fungus. The increased intracerebral pressure in chronic cases of meningitis may produce atrophic changes in the inner table of the skull, but the bone itself is not invaded. Bone lesions of any kind are rare in cryptococcosis, in contrast to the frequency with which they occur in actinomycosis, North American blastomycosis and coccidioidomycosis.

Laboratory Examination.—The leukocyte count is variable and may be normal or slightly elevated. The sedimentation rate is increased and there is usually a mild hypochromic anemia. There are no changes in the chemical constituents of the blood.

The spinal fluid is increased and the fluid may be clear, xanthochromic or turbid. The cell count may be as low as 3 cells or as high as 1000 cells per cu. mm., but more often the count will be between 200 and 800 cells. A pedicle may form The spinal fluid globulin and albumin values usually are increased, giving a specific gravity of about 1.008 The sugar content of the fluid may be normal but generally is decreased. The colloidal gold curve is variable but frequently resembles the meningitic type. The diagnosis is established by finding the organisms either by direct examination or by culture.

MYCOLOGY

Although a single etiologic agent, *C. neoformans*, causes cryptococcosis, there has been some confusion concerning its identity as shown by the imposing list of synonyms (45 to 50) appearing in the literature since Busse's report in 1894. The confusion in terminology is due, no doubt, to the failure to correlate the mycologic findings of this fungus when isolated from vegetative substrates (surface and juice of peaches), from diseases of animals (horse, ox, pig and cheetah) and from diseases of man.

Direct Examination.—Pus from acneform lesions and from subcutaneous tumor-like masses should be aspirated if possible; materials from granulomatous ulcers are best obtained by swabbing the edges Spinal fluid should be centrifuged if no organisms are seen by direct examination Coverslip preparations should be made and examined unstained. It is important that the light be reduced because the capsular material is transparent and difficult to see. If the material to be examined is not purulent or cellular, it is ad-







B

Fig 60 — *Cryptococcus neoformans* *A* Pus containing the round, thick-walled, budding fungus surrounded by capsule × 850 *B* India ink preparation of spinal fluid showing the budding fungus surrounded by capsule × 821

vantageous to place it in a drop of dilute India ink. Such preparations should be examined immediately to avoid artefacts resulting from drying. Frozen sections should be mounted in wet, undiluted Giemsa's stain and examined under a cover glass while the preparation is wet.

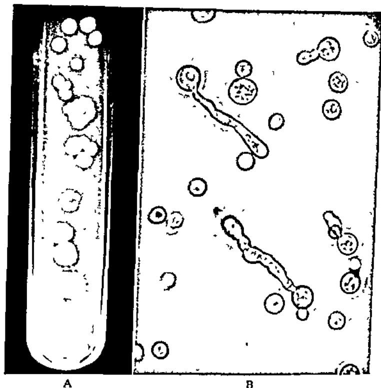


Fig 61.—*Cryptococcus neoformans*. *A*. Primary culture on Sabouraud's glucose agar, twenty-one days, at room temperature from spinal fluid White, wrinkled, granular colonies which on subsequent transfer became a mucoid, tan to brown-colored growth *B* Budding and germinating cells from the granular colonies No capsules were seen in India ink preparations On subsequent transfer, all mycelium was lost and only budding cells with large capsule were seen × 821.

The fungus appears in infected tissue, gelatinous or blood-stained exudate, sputum or spinal fluid as an ovoid to spherical, single-budding, thick-walled, yeastlike organism, 5 to 20 μ in diameter, which is surrounded by a wide, refractile, gelatinous capsule. (Fig. 60 *A*.) The capsule is demonstrated more clearly in India ink preparations (Fig. 60 *B*.)

Cultures.—All materials should be cultured on blood agar and on beef infusion glucose agar at 37° C. and Sabouraud's glucose agar

(Fig. 61 *B*.) In this stage of growth no capsule can be demonstrated. On continued cultivation the typical moist, slimy, mucoid, cream-

... At this time only

seen with short germ tubes in primary isolations, the fungus reproduces by budding only and the cells never form endogenous spores (ascospores).

Colony development at 37° C. on Sabouraud's glucose agar is mucoid and slimy, cream to brownish in color, and sometimes resembles cultures of Friedlander's bacillus. The *microscopic morphology* is identical with that of the mucoid colony grown at room temperature.

Many strains ferment only glucose with acid formation. However, there are too many conflicting data on the biologic activities of this fungus to include sugar fermentations as a method of identification.

Animal Inoculation.—Infected material from the patient should be *injected intraperitoneally* into mice. Saline suspensions of *pure* cultures also should be injected intraperitoneally into mice. Lesions develop slowly and the mouse may not die until after 3 or 4 weeks. Gelatinous masses in the mesentery, enlarged peritoneal nodes and brain tissue will reveal the budding encapsulated fungus on direct examination, the fungus may be cultured from these lesions.

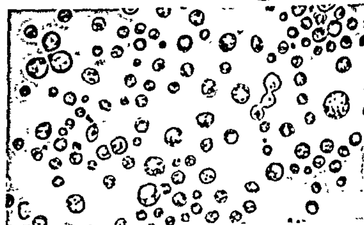
Mycologic Diagnosis.—The *appearance in tissue, sputum or exudate* of spherical, thick-walled, budding organisms surrounded by wide capsules is almost diagnostic for *C. neoformans*. In cultures from sputum or skin, the fungus must be differentiated from saprophytic cryptococci by its ability to grow at 37° C. and by determining its pathogenicity for mice. It is differentiated from other fungi which produce budding, yeastlike cells in tissue (*Blastomyces dermatitidis* and *B. brasiliensis*) by its single bud, its wide capsule and its failure to produce a moldlike growth at room temperature.

Cryptococcus neoformans (Sanfelice) Vuillemin, 1901. *Synonymy.*—*Saccharomyces sp.* Busse, 1894, *Saccharomyces neoformans*









... Culture on Sabouraud's glucose agar, ... from Sabou- ... glucose agar m

Sanfelice, 1895, *Cryptococcus hominis* Vuillemin, 1901; *Torula neoformans* Weis, 1902; *Torula histolytica* Stoddard and Cutler, 1916; *Cryptococcus histolyticus* Castellani, 1928; *Cryptococcus meningitidis* Dodge, 1935; *Debaryomyces hominis* Todd and Herrmann, 1936.

PATHOLOGY

Since cryptococcosis is found most often in the central nervous system or meninges, examination of spinal fluid is more important than histologic examination However, the diagnosis must be made by histologic methods when an intracranial mass or biopsy material is removed.

C. neoformans is one of the most inert of the fungi, and may exist in tissues for long periods of time without stimulating any inflammatory response On the other hand, after a relatively long period of residence in the tissues, a chronic inflammatory response may result. Pus formation is infrequent. Lesions often appear to have a gelatinous consistency due to the overabundance of capsular material produced by the organism

Biopsy.—Lesions from the skin, subcutaneous tissues or bone, usually found in association with generalized or meningeal cryptococcosis, show either an abundant mass of organisms surrounded by the cells of a chronic inflammation and numerous giant cells, or there may be no cellular reaction whatsoever. In SKIN LESIONS, the organisms occur in the absence of miliary abscesses, which is in contrast to the findings in North American blastomycosis. SUBCUTANEOUS LESIONS often appear as tumors and the resemblance to myxoma has been stressed. In several instances, cryptococcosis of LYMPH NODES has presented a histologic appearance strongly [illegible]

presenting a histologic appearance referred to as lymphomatosis. Nodules from the BRAIN SUBSTANCE removed at operation have been shown to be tumor-like masses of the fungus with or without much cellular reaction

In sections prepared from biopsy material and stained by hematoxylin and eosin, the budding organisms surrounded by an abundant capsular material can be identified The fungus cells may occur free in masses or within the cytoplasm of giant cells. The India ink method of demonstrating capsules should be applied to tissues before or after fixation. A freshly cut surface of the biopsy material



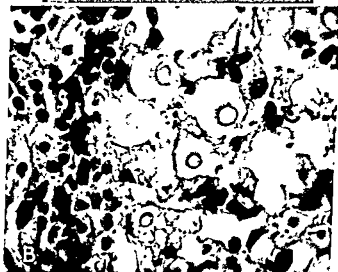


Fig 63.—*A* Cryptococcosis of brain The organisms, essentially devoid of cellular reaction, some budding, separated by mucinous capsular material in a perivascular space. Gram's stain (MacCallum's) × 125. *B* Cryptococcosis of meninges Gray organisms surrounded by non-staining mucinous capsule. Cellular reaction to the left, largely lymphocytic. Subcutaneous lesions have a similar appearance H & E. × 550

should be scraped and the scrapings suspended in dilute India ink. Staining of sections by Gram's method shows that the central portion of the organism inside the mucinous capsule stains intensely blue.

Autopsy.—Cryptococcosis of the BRAIN and MENINGES may be found without evidence of the disease elsewhere in the body. Grossly, the meninges and brain, even in fatal cases, may appear almost normal for the organisms may be dispersed so evenly in the subarachnoid space that cloudiness is scarcely perceptible. Pachymeningitis has been observed but usually only leptomeningitis is present. In some cases, tubercle-like structures occur along the blood vessels and there is a thick exudate at the base of the brain. The cut surface of the brain may be normal, or there may be moderately large cystic spaces. Microscopically, there is considerable variation in different cases. An almost pure culture of the organism may be found (Fig. 63 *A*, *B*), or there may be a chronic inflammatory reaction with giant cells and scar tissue and many other types of inflammatory cells, including macrophages, lymphocytes and eosinophils. Polymorphonuclear neutrophils usually are scarce. The cystic spaces in the brain substance may be merely dilated perivascular spaces continuous with the leptomeninges. Organisms may occur in these cystic spaces as a pure culture, or there may be a chronic inflammatory reaction as in the leptomeninges. The organism is seen easily in sections stained by Gram's method (Fig. 63 *A*), but may be difficult to find in sections stained with hematoxylin and eosin, especially when a chronic inflammatory reaction is present. At times the organisms apparently do not take the stain at all.

Cryptococcosis of the thoracic and abdominal viscera is found most often in connection with cryptococcosis of the central nervous system. There may be hematogenous involvement of lungs, spleen, kidneys and other organs. The reaction is usually a chronic one and tubercle-like structures have been described. In the lungs a miliary form of cryptococcosis may occur. In one instance, an acute inflammatory reaction with acute bronchopneumonia was found. There may be consolidation of the lungs and abscesses may form. Circumscribed and well-defined lesions of firm consistency, resembling tumor masses, have been described as occurring in the lungs.

IMMUNOLOGY

Serology.—Although the literature contains an occasional report describing the presence of agglutinating and complement fixing

antibodies in the sera of infected patients, most observers have failed to demonstrate any serologic evidences of infection, even after extensive vaccine therapy. That the presence of an excessive amount of capsular material may inhibit antibody production is indicated by the investigations of Benham, who failed to produce agglutinins or precipitins in rabbits by the injection of whole yeast cells. Antibodies were formed, however, if the animals were injected with cells from which the capsular material had been removed by chemical methods. The antibodies to the pathogenic cryptococci also agglutinated some strains of non-pathogenic cryptococci isolated from normal skin.

Hypersensitivity.—Focal and local reactions to various *Cryptococcus* antigens have been described, but there is insufficient information concerning the allergic status in cryptococcosis to justify skin testing as a diagnostic procedure. Although vaccines have been tried as therapeutic measures, no beneficial results have been observed.

DIFFERENTIAL DIAGNOSIS

The cutaneous, subcutaneous and glandular lesions usually are diagnosed by routine biopsy and cultures. The pulmonary lesions must be differentiated from tuberculosis, other non-tuberculous infections and mycotic infections of the lungs, especially actinomycosis, North American blastomycosis, coccidioidomycosis and moniliasis. Cryptococcosis of the central nervous system may be mistaken for tuberculous meningitis, encephalitis, brain tumor, brain abscess, dementia psychosis, dementia paralytica, *Brucella* meningitis, *Listerella* meningitis and other mycoses invading the central nervous system, such as actinomycosis, North American blastomycosis, coccidioidomycosis and moniliasis

PROGNOSIS

The local cutaneous or subcutaneous lesions may heal slowly after a number of months, or they may spread to the central nervous system. Primary pulmonary cryptococcosis *usually spreads to produce* generalized disease with cerebral involvement. However, *it is not unlikely that primary pulmonary infection may occur* and heal spontaneously. Until recently, infection of the central nervous system has proved fatal within 3 to 6 months although an occasional patient has been known to live for more than 5 years. The sulfonamide drugs have introduced a ray of hope.

TREATMENT

Central Nervous System Cryptococcosis.—Repeated lumbar punctures are of value in lessening the intensity of symptoms. SULFANILAMIDE and SULFAPYRIDINE were used in the treatment of central nervous system cryptococcosis by Reeves, Butt and Hammack in 1941, who reported recovery of a patient after sulfapyridine administration, but the authors emphasized that this patient was improving before the drug was given. In 1942, Marshall and Teed reported the recovery of a patient following intensive treatment with sulfadiazine.

We have used SULFADIAZINE in the treatment of two cases of primary pulmonary cryptococcosis. There was definite improvement in the pulmonary lesion in one patient (Fig 58) until he became sensitive to the drug and it had to be discontinued. Later, the infection spread to the brain and death resulted. The other patient tolerated sulfadiazine very well and is continuing to improve. (Fig. 59.) Sulfadiazine should be given in doses sufficient to maintain a blood level of 8 to 12 mg per 100 cc. of blood; the drug should be continued for several weeks after the disappearance of symptoms. In Marshall and Teed's patient, several relapses were observed following interruptions in the treatment.

Encouraging results have been obtained in the treatment of localized cutaneous and subcutaneous lesions by EXCISION and DRAINAGE, followed by LOCAL X-RAY treatment, IODIDES by mouth, or both An infection of the knee, reported by Kessel and Haltward, failed to respond to both iodides and x-rays, but no recurrence followed amputation With sulfonamide therapy, it is possible for [illegible] n pro- [illegible] ving to stimulate immunity with a special type of VACCINE prepared by the method described by Benham However, one of our patients was given repeated injections of a vaccine prepared by Benham's method, and no precipitins or agglutinins could be detected in his serum.

Meyer has reported recently that cultures of *C. neoformans* are killed IN VITRO by PENICILLIN in approximately the same doses required to kill *Staphylococcus aureus* Since penicillin does not enter the spinal fluid from the blood, it will be necessary to give it intrathecally, as well as subcutaneously and intravenously, in order to reach the cryptococci in the brain and in the meninges

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Chapter VIII

MONILIASIS

(Thrush, Mycotic Vulvovaginitis, Bronchomycosis)

THE FUNGUS causing moniliasis can be isolated so frequently from the stools, vagina, skin and throats of apparently healthy individuals that a diagnosis of moniliasis often is difficult. Since the organism may be found in sputum from patients with tuberculosis, lung abscess and other pulmonary conditions, a diagnosis of pulmonary moniliasis is warranted only if the fungi can be found constantly on repeated examinations and other etiologic agents are excluded.

Definition.—Moniliasis, caused by species of *Candida*, usually *C. albicans*, is an acute or subacute infection in which the fungus may produce lesions in the mouth, vagina, skin, nails, bronchi or lungs and, occasionally, a septicemia, endocarditis or meningitis



Fig 64 —Moniliasis of tongue and angles of mouth (perlèche-like lesion) showing white patches

Geographic Distribution.—Cases of moniliasis have been reported from all parts of the world, but the fungus occurs so frequently in healthy individuals and in such a variety of clinical forms that it is impossible to obtain accurate data concerning the geographic distribution of the disease.

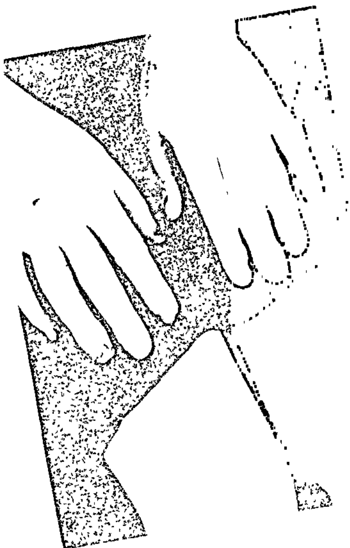
Source of Infection.—Since pathogenic strains of *C. albicans* can be isolated from (1) normal skin, (2) normal oral or vaginal mucous membranes or (3) stools of normal individuals, it is obvious that most infections have an endogenous source; and the determination of the source of infection is as difficult a problem as it is in *Staphylococcus aureus* infections. Occasionally, the infection is contagious and true epidemics have occurred under unusual circumstances Balanoposthitis has been observed in the husbands of women with *C. albicans* vaginitis, and cutaneous moniliasis has occurred around the nipples of mothers nursing infants suffering from oral thrush Epidemics of thrush have occurred in infants, and epidemics of paronychia, intertrigo and perlèche have been reported. Explosive outbreaks of cutaneous moniliasis have been described in fruit packers, in whom the infection occurs on areas of skin macerated by repeated immersions in water.

Age, Sex, Race, and Occupation Incidence.—Moniliasis occurs at all ages, in all races and in both sexes, and certain predisposing factors have been recognized. Oral thrush most frequently occurs in infants and in elderly people with wasting diseases, such as tuberculosis and cancer. Lesions of the hands occur in housewives, bakers, waiters, bartenders and fruit packers whose hands are macerated by frequent soakings in water. Lesions of the tongue and lips are found most often in patients with poorly fitting artificial teeth, and pregnancy and diabetes predispose to *C. albicans* vaginitis. Five cases of mycotic endocarditis have been reported in drug addicts, and in four of these cases the fungus was identified as *C. parakrusei*.

SYMPTOMATOLOGY

The clinical pictures of *C. albicans* infections are so varied, depending upon the location of the infection, that they will be discussed separately under the anatomical sites involved.

Moniliasis of the Mucous Membranes.—Oral infection with *C. albicans* results in the development of the typical creamy white patches of thrush. Such lesions may be seen as single large or multiple small patches scattered over the mucous membranes (Fig. 64) They are loosely adherent to the mucosa and removal of the plaque reveals



a bright red, moist base. In some patients, the mucous membranes are fiery red in color and the superimposed white patches are small and scattered. Such a clinical picture is found most often in patients [illegible]

sides or undersurface of the tongue. The localized lesions are firmly adherent to the tongue, slightly elevated, somewhat corrugated, and suggest a patch of drifted snow. The white patches may be discolored if the patient smokes excessively. *C. albicans* also has been associated with the condition "hairy tongue."

Perlèche is seen as cracks or fissures in the corners of the mouth The lesion is macerated, fissured and eroded, and has a moist, erythematous base. A large series of cases was studied by Finnerud in 1929, and Frank, in 1932, reproduced the disease experimentally in man with pure cultures of *C. albicans*. The predisposing factor may be a *dietary deficiency in which C. albicans, normally occurring in the* mouth, finds suitable conditions for prolific growth.

MONILIA VULVOVAGINITIS is common particularly in diabetes and in [illegible]

thelium is a predisposing factor. The lesions resemble a simple eczematoid dermatitis, or may show excoriated vesicular pustules or, in rare instances, ulceration may occur. Such a type of vaginitis occurs most frequently in the poorer classes, more often in pregnant (15 to 30 per cent) than in non-pregnant (7 to 16 per cent) women and most often in pregnant Negro women (41 per cent) Monilia vaginitis has been reproduced experimentally with pure cultures of *C. albicans* by *Hesseltine, Borts and Plass.*

The investigations of Carter and Jones and of Jones and Martin have demonstrated that *C. albicans* usually is present in cases of vulvovaginitis but that a morphologically similar non-pathogenic organism, *C. stellatoidea*, predominates in patients without symptoms of vaginitis

Cutaneous Moniliasis.—Three clinical types of infection are seen: (1) localized lesions, (2) generalized lesions and (3) moniliids. The disease is seen frequently in diabetics and in individuals whose occupations predispose to frequent immersions in water. Obesity, alcoholism vascular stasis and profuse sweating are some of the additional predisposing factors

pyogenic lesions but which do not contain pus. The nail becomes hardened, thickened and grooved and sometimes assumes a brownish color; but it retains much of its luster and does not become brittle, and débris does not accumulate beneath the nail as happens in tinea ungium.

INTERTRIGO due to *C. albicans* (Fig. 67) is characterized by well-marginated, erythematous, exudative patches with papulosquamous borders which may be rimmed by vesicles and small pustules. The commonest sites of intertrigo are the axillae, inframammary areas, umbilicus, gluteal folds and groin. Occasionally, the webs of the toes are involved by the fungus, and the lesions may resemble the macerative type of tinea pedis caused by the filamentous dermatophytes

PERIANAL MONILIASIS produces pruritus ani of the white macerative type and may resemble the soggy type of infection caused by members of the dermatophyte group of fungi.

GENERALIZED CUTANEOUS MONILIASIS is very resistant to treatment. The lesions appear on the glabrous skin (Fig. 68) and are associated, as a rule, with glossitis, stomatitis, paronychia or other types of localized infection The infection almost always involves the inframammary areas, the umbilicus and the gluteal folds, the lesions may be eczematoid in type or may be covered with vesicles or pustules.

The MONILIIDS or "levurids" are sterile, grouped vesicular lesions which may be found over the hands and body. Such lesions have the same clinical characteristics as the dermatophytids which are described in another section.

Bronchopulmonary Moniliasis.—Bronchial moniliasis is not uncommon. A particular type of infection occurs in the tea-tasters of Ceylon and has been described in detail by Castellani. Cough is the most characteristic and distressing symptom; the health of the patient is not affected seriously. The sputum is almost colorless, but mucoid and gelatinous, and frequently contains small gray flakes composed of budding fungus cells and cellular detritus. The infection sometimes disappears spontaneously, but often lasts for years with periodic progressions and retrogressions. In bronchial moniliasis, the physical signs are those of bronchitis with medium and coarse rales at the bases of the lungs

X-RAYS.—Films of patients with bronchial moniliasis usually show little more than a non-specific type of peribronchial thickening. Some-





Fig 68 —Moniliasis of face and axilla (Courtesy of Dr John H Stokes)

times a peculiar hazy type of linear fibrosis can be seen Although such a picture is not diagnostic, Dr. Robert J Reeves, of Duke Hospital, often suggests the possibility of moniliasis, and cultures very frequently have confirmed his tentative diagnosis.

Pulmonary Moniliasis.—Pulmonary moniliasis is not as common as the bronchial form, but is a more serious disease. The temperature and pulse are elevated moderately, pleural pain is common and effusion occurs occasionally. Cough is harassing and the patient produces mucoid, gelatinous sputum which sometimes is blood streaked. A purulent sputum indicates that secondary infection with pyogenic cocci probably has occurred.

There is a patchy, or bronchopneumonic, type of infection which usually is scattered over two or more lobes. Medium moist rales are present over the areas of involvement, but dulness and changes in the breath sounds are rare. The more severe infections have the physical signs of confluent or lobar pneumonia with dulness, increased tactile fremitus, whispered voice and prolongation of the expiratory sound. Medium moist rales usually are present.

It is probable that many of the lesions of pulmonary moniliasis heal spontaneously and completely, but in other instances recovery is not complete and the patient may develop the clinical picture of the chronic bronchial type. Death may occur when two or more lobes are involved with a dense pneumonic process

X-RAYS.—The shadows seen in pulmonary moniliasis vary in size and shape, and resemble those seen in bronchopneumonia except that the edges of the lesions are less sharply defined (Fig 69.) Two or more lobes frequently are involved although the apices of the lungs usually are spared The lesions are rather labile, and films made at weekly intervals show definite evidences of clearing in some areas and spreading in others In very severe infections, the massive lesions are dense and smooth and often may involve almost an entire lobe (Fig 70) Some lobes may show almost complete consolidation, while others contain only bronchopneumonic patches

BONE AND JOINT INFECTIONS are very rare but have been reported

ENDOCARDITIS has been reported in drug addicts, the symptomatology and course of the disease being similar to that of subacute bacterial endocarditis caused by *Streptococcus viridans* The fungus isolated from four of the five cases was C *parakrusei*, an organism which is not pathogenic for laboratory animals

Laboratory Examination.—There usually is no leukocytosis and the sedimentation rate is normal or only slightly increased in bron-



Fig 69 —Moniliasis of the lungs. There are diffuse nodular lesions throughout the right lung and in the center of the left lung



Fig. 70 —Moniliasis of the lungs There is a smooth homogenous lesion in the right upper lobe, a similar process is beginning in the left upper lobe

tissues may be that of chronic inflammation with giant cells or abscess formation. Necrotic areas may be present, and ulceration of the epithelium with marked "round cell" infiltration may be noted

In microscopic sections, the organisms appear as mycelial threads and blastospores. Staining of the mycelial threads is very faint in hematoxylin and eosin sections, and the blastospores usually are not identified since they can be confused with lymphocytes or other cells However, staining of the sections by Gram's method brings the fungus elements into prominence and they are identified with ease In Miale's case, the fungi were present in the areas of deep necrosis and in the centers of the tubercle-like structures. The mycelia were slender rods a few microns thick, the walls of which stained darkly The gram-positive material gave them an irregularly segmented or beaded appearance The blastospores were identified easily when they occurred in clusters, while the individual cells were difficult to find They appeared as small, ovoid cells about 4 μ in diameter, stained darkly gram-positive and showed a thin, doubly refractile capsule which took the counter stain poorly. The fungus organisms were not acid-fast. The advisability of applying Gram's method of staining is apparent; any of the technics for the gram-staining of tissue sections may be used. MacCallum's modification of Goodpasture's gram stain is satisfactory and is described in the appendix (p. 320). A definite diagnosis of moniliasis from microscopic sections alone should not be made, and part of the biopsy material should be cultured.

Autopsy.—In some instances, the correct clinical diagnosis can be established only at autopsy

In the case reported by Miale, the infection had started as a chronic granulating process which involved the buccal surfaces of the mouth and pharynx Later the eye became infected At autopsy, monilial laryngitis also was demonstrated but no lesions were found in the lungs. Death was due to meningitis There was a thick exudate at the base of the brain over the pons and peduncles Tubercle-like structures, less than 1 mm in diameter, were present in this exudate and along the vessels on the lateral aspects of the brain The ventricles were dilated slightly and showed numerous nodules Sections of these nodules showed giant cells containing blastospores of *C. albicans* Sections from the brain also showed branching segmented and beaded mycelia Blastospores were present but were not identified easily. The diagnosis was confirmed by culture

In Rockwood and Greenwood's case, the diagnosis was made before autopsy The patient had spectacular skin lesions involving

almost the whole body, hyperkeratosis of the hands and subcutaneous abscesses without involvement of the viscera.

Monilial endocarditis has occurred; most of the cases reported have been in drug addicts who took narcotics intravenously. The lesions consist of massive vegetations, localized to one portion of the circumference of a valve, and resemble the findings in bacterial endocarditis. Yeastlike cells have been demonstrated in the vegetations in great numbers in at least one patient. Such an endocarditis may be associated with systemic moniliasis.

IMMUNOLOGY

Serology.—Agglutinins have been demonstrated in the sera of patients with moniliasis, and titers as high as 1:2400 have been reported. However, we frequently have failed to find agglutinins in patients with rather severe infections, and do not consider the agglutinat on reaction as a valuable diagnostic procedure. Saline suspensions of the yeast cells made from the growth on Sabouraud's media are smooth and homogenous, but somewhat granular, and the clumps produced by human antibodies usually are so fine that it is quite difficult to determine whether or not the cells are agglutinated.

In contrast to sera from patients, the sera of hyperimmunized rabbits are able to agglutinate the yeast cells and produce large, heavy floccules. By using rabbit sera, it has been shown that there is such a close antigenic relationship among the various species of *Candida* that serologic methods alone cannot be relied upon in species identification.

Hypersensitivity.—A large percentage of apparently normal individuals give positive skin reactions when injected intracutaneously with vaccines or extracts of *C. albicans*. Such findings are not sur-

or not the patient is hypersensitive to the fungus.

DIFFERENTIAL DIAGNOSIS

The diagnosis of ORAL, VAGINAL, and CUTANEOUS INFECTIONS with *C. albicans* is relatively simple since the organisms usually are seen in the fresh preparations and can be cultured without difficulty. Direct examination is the only practical way of differentiating moni-

liasis from the lesions caused by the common dermatophytes, seborrheic dermatitis, contact dermatitis, avitaminosis, sprue, geographic tongue and pyodermia. In patients with moniliids, the diagnosis depends upon the clinical characteristics of the lesions and upon the demonstration of hypersensitivity in the patient.

The diagnoses of BRONCHIAL and PULMONARY moniliasis must be made with considerable caution since the isolation of *C. albicans* from the sputum does not justify in itself a diagnosis of moniliasis. Since *C. albicans* can be grown from the saliva of normal individuals, the presence of the fungus in the sputum may be coincidental. The problem is complicated further by the fact that *C. albicans* frequently is a secondary invader in bronchial and pulmonary diseases. Shrewsbury analyzed many of the reported cases in the literature and concluded that most of them were instances of "secondary thrush" of the bronchi. We have found *C. albicans* to be a secondary invader in primary carcinoma of the lung, pulmonary tuberculosis, pneumococcus pneumonia, asthma, pulmonary abscess, bronchiectasis and congestive heart failure. The presence of agglutinins, precipitins or complement fixing antibodies is proof of invasion of the body by the organism, but does not establish whether the invasion is primary or secondary although such evidence is more in favor of a primary invasion. The diagnosis can be made with a reasonable degree of certainty if *C. albicans* is present CONSTANTLY AND IN LARGE NUMBERS in sputum freshly coughed up from the lungs and if the patient responds promptly to specific treatment. The presence of antibodies in the serum adds to the certainty of the diagnosis, but their absence does not rule out moniliasis

PROGNOSIS

[illegible] generalized cutaneous moniliasis or hypersensitive patients with moniliids are extremely resistant to treatment, and [illegible] monary moniliasis occasionally is fatal The prognosis is hopeless in patients with endocarditis or meningitis

TREATMENT

The frequency with which moniliasis occurs in marasmic infants and debilitated adults emphasizes the necessity of restoring the patient's general resistance with a well-rounded diet which contains an abundance of vitamins. All factors which predispose to maceration, such as soap and water, ill-fitting dentures and excessive sweating, must be corrected. Diabetics must be regulated. A low carbohydrate diet is necessary and the weight should be reduced if obseity is present.

The ORAL lesions often respond to alkaline mouth washes GENTIAN VIOLET, diluted 1:10,000 in 10 per cent alcohol, may be painted on the areas involved, and the treatment may be supplemented by gargling with a 1:100,000 solution of the dye. The gentian violet treatment should be repeated every 6 to 12 hours for four or five days and then stopped to avoid irritation of the mucosa.

In many instances MONILIA VULVOVAGINITIS is improved by treatment with alkaline douches. GENTIAN VIOLET, diluted 1:10,000 and given weekly, biweekly or every other day, has been effective in some of the resistant cases. Hesseltine employs LUGOL'S SOLUTION, diluted to one-fourth strength, as a topical application to the vagina once each week, and supplements this treatment by having the patient insert into the vagina each night 2 capsules containing a mixture of potassium iodide and potassium iodate (6.2 parts of potassium iodide to 1 part of potassium iodate). Capsules of 00 to 000 size are employed; the drugs are mixed and diluted with kaolin so that each capsule contains approximately 0.125 Gm of the iodides. Occasionally, a case of vaginitis which has resisted other types of treatment will improve rapidly when given an autogenous vaccine.

Topical therapy of cutaneous moniliasis depends on the location of the lesion Onychia and paronychia are treated by 1.4000 POTASSIUM PERMANGANATE soaks 3 times daily, followed by application of 1 per cent GENTIAN VIOLET SOLUTION. AMMONIATED MERCURY OINTMENT (5 per cent) may be used and should be rubbed in well The same treatment may be applied to most intertriginous areas. In resistant cases, fractional X-RAY THERAPY may be used; a dose of 75 roentgen units, unfiltered, should be given to the affected areas at weekly intervals for 4 to 8 weeks. VACCINE DESENSITIZATION with oidiomycin, as described under trichophytin desensitization, may be required to combat successfully the more resistant infections.

BRONCHOPULMONARY MONILIASIS responds readily, as a rule, to treatment with POTASSIUM IODIDE The iodides should be given by the

rapid method described in the chapter on blastomycosis (p. 48) ETHYL IODIDE inhalations were employed successfully by MacKee in treating an apparently hopeless case of the systemic type of moniliasis. Before the iodides are administered, the patient should be given a skin test with a heat-killed *C. albicans* vaccine to determine the degree of sensitivity to the fungus. Hypersensitive patients should be desensitized before iodides are administered; the dilutions and doses are calculated in the manner described in the chapter on North American blastomycosis (p. 47).

INTRAVENOUS GENTIAN VIOLET has been recommended by Stovall and others in the treatment of PULMONARY MONILIASIS The dose of gentian violet is 5 mg. per kilogram of body weight, and it may be repeated daily or every other day for seven to ten days. Reactions can be avoided if commercially prepared solutions are used, but a solution made in the laboratory is safe if the concentration does not exceed 0 5 per cent and the solution is filtered through a Berkefeld or a Seitz filter. Thrombosis of the veins occurs in patients who are injected with more concentrated solutions of the dye.

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Fig 74 —Geographic distribution of histoplasmosis

Chapter IX

HISTOPLASMOSIS

HISTOPLASMOSIS rarely has been diagnosed before autopsy. The organism in the tissues has an appearance superficially resembling the protozoal bodies seen in leishmaniasis, and the clinical picture of histoplasmosis has certain features which are not unlike those seen in kala-azar

Definition.—Histoplasmosis, caused by *Histoplasma capsulatum*, is an infection characterized by emaciation, leukopenia, anemia and irregular pyrexia There is frequently lymphadenopathy, splenomegaly, hepatomegaly and ulcerations in the naso-oral-pharyngeal cavities and intestines

Geographic Distribution.—Histoplasmosis has been reported from Central America, South America, the United States, England, the Philippines, Java and South Africa. (Fig 74)

Source of Infection.—The organism apparently enters the body through the mouth or the intestinal tract, and primary lesions on the lip, tongue and larynx have been described. In a few cases the first lesion noted was a cutaneous ulcer, suggesting that the fungus has the ability to enter the body through the skin. Enlargement of the mesenteric lymph nodes has been noted in many of the cases studied at necropsy, and extensive ulceration in the intestinal mucosa is a frequent finding The ability of the fungus to survive exposure to the gastric juice has been demonstrated by de Monbreun, who succeeded in infecting young dogs by feeding them cultures of *H capsulatum*

Occasionally, the first evidence of the disease is seen in a lymph node, a knee joint or in one of the internal organs. Although the lungs were involved in 11 out of 50 reported cases, pulmonary invasion occurs usually as a part of the generalized disease and not as a primary infection.

Histoplasma capsulatum has not been found in nature, but de Monbreun isolated, from a spontaneous infection in a dog, a fungus which was indistinguishable from strains isolated from patients. Since approximately one-fifth of the cases have been described in infants less than 2 years of age, it is possible that dogs, or other domestic pets, may be carriers of the disease or that the organism

exists in some focus in or about the home where dogs and young children can be infected easily.

Age, Sex, Race, and Occupation Incidence.—The disease may be encountered at any age from 3 months to 70 years. In a series of forty-eight cases, four were 6 months or younger, four were between 6 months and 1 year, five were from 1 year to 10 years, two between 10 and 20, four between 20 and 30, five between 30 and 40, eleven between 40 and 50, seven between 50 and 60 and six between 60 and 70 years of age. Approximately 28 per cent of the cases have been reported in children less than 13 years of age. In forty-eight instances, thirty-five were in males and only thirteen in females, but the disproportion between the sexes was not so striking in children where there were eight males and five females. The disease has been found in whites in the United States and in Negroes, Javanese, Chinese and Filipinos. No information is available regarding occupational predisposition.

SYMPTOMATOLOGY

Darling originally described the disease as characterized by chronicity, fever, emaciation, anemia, leukopenia and splenomegaly. As more patients have been studied, it has been recognized that the symptomatology is more complex, especially in cases in which there is an extensive involvement of one organ or one system.

The duration of the disease has varied from 3 weeks to 8 months Occasionally, a patient may remain chronically ill for years and then die within a few weeks following a dissemination of the disease. Young children rarely live more than several weeks after the onset of the infection

In CHILDREN, the onset usually is insidious with gradual development of fever, digestive disturbances, diarrhea and loss of weight. There is a progressive enlargement of the liver and spleen and anemia and leukopenia develop The external lymph nodes usually are palpable but marked lymph node involvement is not seen in children, in contrast to the extensive lymphadenopathy occurring in some of the adult cases. Infection of the lymphoid tissue of the intestines is common, and extensive ulcerations frequently are found at necropsy. Although one child had an ulcerated lesion in the nose, it is thought that the most common portal of entry in children is the intestinal tract, explaining the local ulcerations and the common findings of mesenteric adenitis, hepatomegaly and splenomegaly The lungs may show enlargement of the hilar lymph nodes and small subpleural nodules probably resulting from terminal dissemination The bone

marrow may be extensively involved, accounting for the anemia and leukopenia, and the relative lymphocytosis may be explained by the infection of the lymph nodes. Purpura has been noted in several cases. With terminal bacterial pneumonia, there may be a superimposed leukocytosis.

The disease in ADULTS may follow the same pattern as in children, with fever, loss of weight, diarrhea, anemia, leukopenia, hepatomegaly and splenomegaly; but the disease, as a rule, runs a more chronic course lasting for a period of months Sometimes the intestinal symptoms predominate, and the diagnosis of amebiasis has been made wrongly although gross blood rarely is seen in the stools The liver and spleen may not be enlarged if the portal of entry is not the intestinal tract Ulcers of the TONGUE were the first lesions noted in two cases and were followed by ulcerations in the mouth and pharynx and cervical lymph node enlargement

In one instance, reported by Crumrine and Kessel, *H. capsulatum* was found in the purulent discharges from OTITIS MEDIA. In another case, otitis media was followed by the development of ulcerative lesions in the mouth and large masses of matted lymph nodes in the neck, this patient had a severe neutropenia (leukocytes 1,900) and moderate anemia in the absence of a palpable liver and spleen At necropsy, 6 months later, there were no evidences of intestinal infection and the liver and spleen were enlarged

In several patients, the presenting lesion was an extensive progressive ulceration of the PHARYNX or LARYNX A number of other patients gave a history of hoarseness as the initial symptom although no causative lesions were demonstrated. Small mucosal ulcerations are not infrequent in the mouths of both children and adults as a part of the terminal picture.

Occasionally, the primary symptoms are pulmonary, and in the case reported by Phelps and Mallory the necropsy showed pulmonary infection only At autopsy, in Humphrey's second case, nodules were found in the left upper lobe, and in one of the nodules the mycelial stage of the fungus was found The intestines were normal, but the liver and spleen were invaded and it was impossible to determine whether the lung lesions represented the primary form of infection or resulted from dissemination from some other focus The lungs practically always are infected in generalized cases. The lesions are multiple but small, frequently pleural or subpleural, and often cause pleural pain. Hemoptysis has been observed in only one patient. Physical examination reveals only rales at the bases.

An ulcer on the LIP was the presenting symptom in the case reported by Palmer, Amolsch and Shaffer. (Fig. 75.) At necropsy, there was extensive ulceration of the entire larynx, including the vocal cords. The spleen was infected and there were caseous lesions in both adrenals. The liver was not enlarged, and the intestinal tract was essentially normal.



Fig 75.—Histoplasmosis. Note mucocutaneous lesions on lip and penis. (After Palmer, Amolsch and Shaffer, Archives of Dermatology and Syphilology, 45)

An infection of the KNEE was the presenting symptom in the case reported by Key and Large X-rays showed a destructive process in the lower end of the femur (Fig 76) and bilateral, symmetrical, dense lesions occupying the central two-thirds of both lower lung lobes The leg was amputated and the diagnosis established. The patient

died, but necropsy was refused and the specificity of the pulmonary lesion could not be determined.

Sometimes the infection begins as a small SKIN lesion and widespread ulcers of the skin may develop.



Fig 76 —Histoplasmosis of the knee The leg was amputated and *Histoplasma capsulatum* was isolated from the lesion (After Key and Large, Journal of Bone and Joint Surgery, *24*)

Presumably, the portal of entry may be through the nasopharynx without the development of a recognizable lesion in cases where the presenting symptom is a striking LYMPH NODE ENLARGEMENT, simu-



lating tuberculous adenitis, Hodgkin's disease, leukemia or lymphosarcoma.

A case of endocarditis caused by *H. capsulatum* has been studied at the Mayo clinic. The organism has been found in the PROSTATE and in enlarged necrotic ADRENALS The adrenals are infected frequently in patients with the generalized disease.

X-rays.—The usual picture is one of slightly enlarged hilar lymph nodes with some peribronchial thickening In a few cases, nodular lesions in the lungs have been described. Key and Large have reported small destructive lesions in the lower end of the femur.

Laboratory Examination.—The bone marrow is infected in nearly all cases of histoplasmosis, resulting in a progressive hypochromic anemia and leukopenia. In most instances, the differential formula is normal but sometimes there is neutropenia or a recurrent type of agranulocytosis. There may be a relative or absolute lymphocytosis, especially in children; and this blood picture, occurring in a child with hepatomegaly and splenomegaly, sometimes had led to an incorrect diagnosis of leukemia or aleukemic leukemia. In one patient an enlarged spleen was removed because of the diagnosis of splenic anemia. In a series of ten reported cases, the erythrocytes varied from 3,800,000 to 1,700,000 with an average of 2,600,000. The hemoglobin content varied from 35 to 85 per cent. The white blood count was 11,640 in one patient; between 6,000 and 8,000 in two patients; between 1,500 and 6,000 in five others; and the remaining two patients had counts of less than 1,500.

MYCOLOGY

H. capsulatum differs from all other fungi pathogenic for man in that the organism is primarily a parasite of the reticulo-endothelial system and rarely is found extracellularly in tissue. At first the organism was thought to be a protozoan, related to *Leishmania donovani* but lacking a blepharoplast. Budding forms eventually were found which indicated that the organism might be a fungus, and this view was proved correct by subsequent cultural studies.

Direct Examination.—Thick and thin smears of peripheral blood and sternal bone marrow should be stained with Wilson's, Wright's or Giemsa's stains. Material from biopsied lymph nodes or from splenic punctures also should be smeared and stained. (Fig. 77.) Fresh and stained preparations of material from ulcerations of the naso-oral passages should be examined carefully.

The fungus appears as a small (1 to 5 μ), oval body in the large

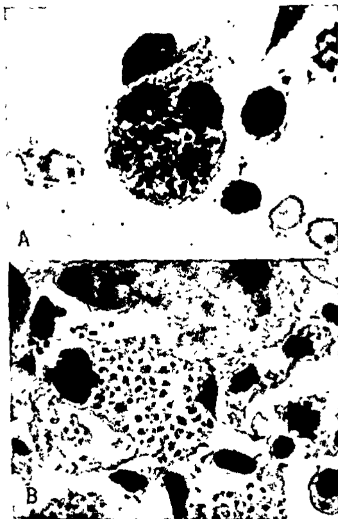


Fig 77.—Histoplasmosis *A* Parasitized mononuclear cell in a peripheral blood smear, × 1300. *B*. *Histoplasma capsulatum* in macrophages in liver × 1300.

mononuclear cells; occasionally budding organisms can be demonstrated.

Cultures.—Suspected materials should be cultured on beef infusion glucose broth, on blood agar to be incubated at 37° C. and on



Fig 78.—*Histoplasma capsulatum* *A* On blood agar, six days, at 37° C. *B* From blood agar culture × 700

Sabouraud's glucose agar to be kept at room temperature All cultures should be held for at least one month before discarding them as negative. In beef infusion glucose broth, the growth is noted first as single or multiple, small, floccose masses dispersed throughout

the liquid. Microscopic examination shows the growth to be composed of branching, septate hyphae with little, if any, spore production

On blood agar at 37° C., the growth becomes evident as moist, scattered, dull white colonies (Fig. 78*A*.) Microscopically, these

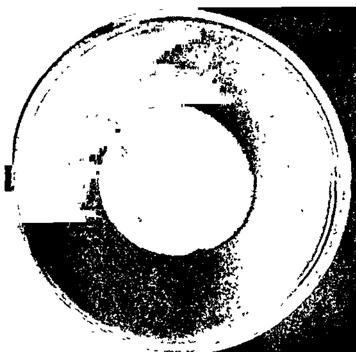


Fig 79—*Histoplasma capsulatum* On Sabouraud's glucose agar, twenty-three days, at room temperature

colonies consist of small (1 to 5 μ), oval, budding cells similar to those found in tissues (Fig 78*B*) Mixed with these cells are short fragments of mycelium which show that the fungus is attempting to go into the mycelial phase If frequent transfers are made to fresh media, the fungus can be maintained in the yeastlike stage which grossly may resemble the growth of *Staphylococcus aureus*

On Sabouraud's glucose agar at room temperature, the fungus grows slowly, producing a white, cottony aerial mycelium which later turns buff to brown in color. (Fig. 79.) Microscopically, these cultures show branching, septate hyphae bearing small, round to pyriform, smooth spores (2.5 to 3 μ in diameter) on short lateral branches or sessile on the sides of the hyphae. (Fig. 80*A*.) At this time the culture may be mistaken for *Blastomyces dermatitidis*. Eventually, however, the characteristic round to pyriform, tuberculate chlamydospores (7.5 to 15 μ in diameter) develop and the mycologic diagnosis is established. (Fig. 80*B*.) Occasionally it has been possible to convert the mycelial phase to the yeastlike phase by transferring to fresh media, sealing the tubes to conserve moisture and incubating the cultures at 37° C.

Animal Inoculation.—Infected material should be injected intraperitoneally into guinea pigs and mice. Cultures in the yeastlike phase or mycelial phase can be inoculated into guinea pigs and mice with the production of lesions in the visceral organs, from which material for examination or culture may be obtained

Mycologic Diagnosis.—*The finding of intracellular, oval, yeastlike* fungi in mononuclear cells of peripheral blood smears, bone marrow smears or smears of material from splenic puncture is diagnostic. Such materials should be cultured to demonstrate the characteristic large, tuberculate *chlamydospores found in the mycelial phase of the*

latum and *B. dermatitidis* buff to brown in color. *The rate of growth of H capsulatum, however, is somewhat slower.* In young cultures, the small, smooth-walled, round to pyriform spores of *H. capsulatum* may be confused with those produced in cultures of *B dermatitidis*. The development of the large, round to *pyriform, tuberculate chlamydospores in H. capsulatum*, however, clearly distinguishes this fungus from any other pathogenic organism.

Histoplasma capsulatum Darling, 1906. Synonymy.—*Cryptococcus capsulatus* Castellani and Chalmers, 1919, *Torulopsis capsulatus* Almeida, 1933; *Posadasia capsulata* Moore, 1934; *Posadasia pyriforme* Moore, 1934; *Histoplasma pyriforme* Dodge, 1935.

PATHOLOGY

Histoplasmosis manifests itself usually as a generalized disease with involvement of the reticulo-endothelial system, but localized lesions may overshadow or occur in the absence of generalized

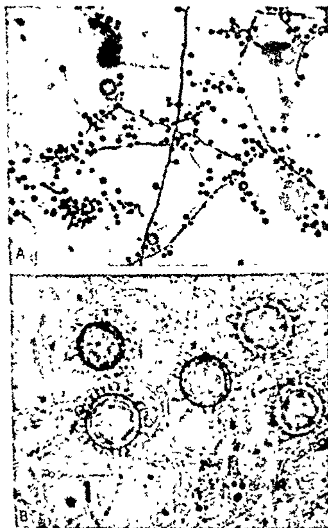


Fig 80—*Histoplasma capsulatum* from Sabouraud's glucose agar *A* Small smooth, round to pyriform conidia × 600 *B* Large, thick-walled, round tuberculate chlamydospores × 1150

involvement. Study of sections may be of the greatest aid in clinical diagnosis since examination of the blood has in several cases failed to show the organisms which subsequently were demonstrated in biopsy material

Biopsy.—Biopsy material from finely nodular or ulcerative lesions of the buccal cavity, larynx, skin or rectum, as well as material from enlarged lymph nodes, has revealed the presence of the fungus in various reported instances. Lesions accessible to biopsy have been reported in the nasal cavity. In these sites, the organism usually is found intracellularly in macrophages with the same appearance which it displays in the internal organs (Fig. 77B), but the fungus may occur in giant cells. Caseous necrosis develops at times and abscess formation has been reported, but this is not a frequent finding. *H. capsulatum* occurs in cells in the yeast form and can be seen in sections stained with hematoxylin and eosin. An exceptional case has shown the mycelial form of the fungus.

In MICROSCOPIC SECTIONS, the morphology of the organisms is not seen as well as it is in SMEARS made from the blood or from organs The Gram's stain applied to sections is valuable because the central portion of the organism stains intensely. The parasite usually measures from 1 to 3 μ in diameter, and basic staining material occurs as a mass surrounded by a capsule. By study with the oil immersion lens, differentiation from the protozoal organisms of leishmaniasis can be made In leishmaniasis, the organism is slightly larger and the linear-shaped kinetoplastic substance can be seen in the organism A third organism to be differentiated from *H capsulatum* in sections is the etiologic agent producing toxoplasmosis

Autopsy.—Autopsy has given the first indication of the nature of the disease in many of the reported cases. Enlargement of the liver and spleen may be the only gross abnormality noted In such cases, the cells of the reticulo-endothelial system, especially those in the spleen, liver and lymph nodes, have phagocyted the fungi like a foreign body and intracellular multiplication of the organisms has occurred.

In many cases necrosis of tissue and tubercles will be present. Necrotic foci may be bordered with macrophages containing the organisms in very large numbers, and the necrosis often appears to consist of death of both the organisms and phagocytes, especially in foci rich in macrophages containing the parasites. Tubercles may occur in the lungs, liver, spleen and kidneys, and caseous necrosis of the adrenal gland is not rare. Ulcerating intestinal lesions and buccal

and laryngeal lesions are impressive in some cases. While the lungs invariably are infected in systemic histoplasmosis, the lesions usually are microscopic in size.

Histoplasmosis may be encountered in connection with other diseases, particularly tuberculosis.

In taking tissue for histopathologic study, provision always should be made to get materials for culture.

IMMUNOLOGY

Serology.—Pernis, Benson and Holinger failed to demonstrate either precipitating or complement fixing antibodies in the sera of their patients, and we have been unable to find any other reports in which serologic studies were made.

Hypersensitivity.—Pernis, Benson and Holinger obtained both an immediate reaction and a delayed tuberculin-like reaction in a patient injected intracutaneously with filtrates prepared from broth cultures of *H capsulatum*. Immediate wheals were produced in this patient and in infected mice by cutaneous injection of material precipitated from broth filtrates by acetone These results have not, as yet, been confirmed or evaluated.

DIFFERENTIAL DIAGNOSIS

Histoplasmosis should be suspected in febrile patients showing anemia and leukopenia, epecially if accompanied by lymphopathy, hepatomegaly or splenomegaly To establish the diagnosis, the organism should be demonstrated in or cultivated from the blood, sternal bone marrow, sputum, lymph nodes or other biopsy material Meleney suggests that the thick blood smear technic should be used in diagnosis Citrated blood should be centrifuged and smears made from the buffy coat layer and from the bottom of the tube where heavily parasitized cells might be found, as in kala-azar

Animal inoculation may be positive when cultures are negative Monkeys, young dogs, young mice, rats, guinea pigs and rabbits have been found susceptible to experimental infection

Meleney reports that the formol-gel and water precipitation tests on the patient's serum, commonly used in kala-azar, were negative in Dodd and Tompkin's patient but were positive in the case studied by Mantell and Troy He also suggests that Ray's globulin precipitation test, used in kala-azar, should be investigated as a possible diagnostic procedure

The dermal and nasopharyngeal ulcers must be differentiated from cutaneous leishmaniasis and the generalized cases, with hepatomegaly and splenomegaly, from visceral leishmaniasis.

Cutaneous, aural, mucosal, nasopharyngeal and laryngeal lesions, with or without lymph node enlargement, may suggest syphilis, tuberculosis, neoplasm, Vincent's angina, tularemia, toxoplasmosis, sporotrichosis, actinomycosis, North American and South American blastomycosis, coccidioidomycosis, cryptococcosis or moniliasis When marked enlargement of the lymph nodes is present, Hodgkin's disease, lymphosarcoma or leukemia should be considered.

The primary pulmonary cases resemble tuberculosis or one of the other pulmonary mycoses. Meleney found *H. capsulatum* as a concomitant or secondary infection in two instances of pulmonary tuberculosis.

The presence of progressive anemia and persistent leukopenia suggests malaria, splenic anemia, Gaucher's disease, aleukemic leukemia, acute benign lymphoblastosis (infectious mononucleosis) or brucellosis.

Cases with striking gastro-intestinal symptoms have been diagnosed incorrectly as tuberculous peritonitis or amebic dysentery.

PROGNOSIS

All reports in the literature indicate that histoplasmosis is always fatal. Children rarely live longer than a period of weeks, and adults usually die after 3 to 8 months. Occasionally, a chronic form of the disease is observed in which the patient has exacerbations of the infection over a period of years In some of the more recent necropsies of adults there is evidence that healing by fibrosis may occur, which suggests the possibility that patients with limited, clinically unrecognizable lesions may recover.

TREATMENT

Iodides, iodized metals, roentgen radiation, bone marrow extracts, liver extracts, pentonucleotide, neoarsphenamine and sulfonamides have been tried without effect.

Meleney advises the use of antimony salts such as POTASSIUM ANTIMONY TARTRATE, trivalent organic preparations such as FUADIN, or pentavalent preparations like NEOSTAM. Definite clinical improvement was obtained in one patient treated with neostam by Mantell, Troy and Kendall Palmer, Amolsch and Shaffer gave five injections

of neostam (stibium chloride) over a period of 10 days. The drug was tolerated poorly and finally was refused by the patient, but at necropsy *H. capsulatum* could not be demonstrated in the tissues although it had been found previously in large numbers in a biopsy specimen. The authors suggest that their patient may have died of acute adrenal insufficiency since both adrenals had been involved by a necrotizing process. Since the adrenals frequently are infected, the possibility of adrenal insufficiency should be kept in mind.

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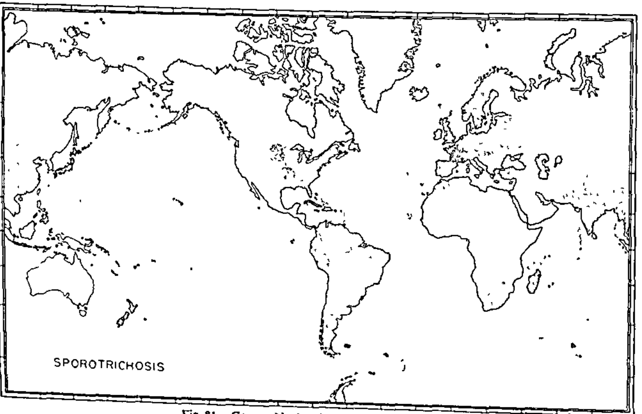


Fig. 81.—Geographic distribution of sporotrichosis.

Chapter X

SPOROTRICHOSIS

SPOROTRICHOSIS presents such a characteristic picture, as a rule, that the diagnosis can be established by the clinical findings alone. Of all the fungus diseases of man, sporotrichosis responds best to treatment with the iodides.

Definition.—Sporotrichosis is a chronic infection caused by *Sporotrichum Schenckii*, and is characterized by the development in the lymph nodes, skin or subcutaneous tissues of nodular lesions which soften and break down to form indolent ulcers

Geographic Distribution.—Sporotrichosis has been reported from all continents. In North America, the disease appears to be more prevalent in the North Central part of the United States, in Europe, most of the cases have been reported from France The widespread distribution of the disease may be seen in the accompanying map (Fig 81) which was based on examination of titles of articles and the names of the medical journals publishing articles on sporotrichosis

Source of Infection.—All available evidence suggests that man acquires sporotrichosis from contact with plants, although the disease may be contracted from infected animals or animals that are acting merely as mechanical carriers. Benham and Kesten have found carnations infected with species of *Sporotrichum* which were not pathogenic for animals, however, they succeeded in infecting carnations with *S Schenckii* isolated from man Gougerot found a strain of *Sporotrichum* growing saprophytically on plants in the French Alps, this fungus was indistinguishable morphologically from strains isolated from human sources and was highly pathogenic for rats after repeated animal passage In ten of Foerster's eighteen cases, the disease developed after injuries caused by thorns of the barberry shrub In two patients, a thorn was removed from the initial lesion, and in six other cases the patient had had thorns removed from the finger preceding development of the disease

Spontaneous sporotrichosis has been found in horses, dogs, cats, rabbits and rats Pathogenic sporotricha have been found in the mouth and on the fur of healthy rats, and Meyer recovered it from the coats of horses, some of which were suffering from sporotrichosis,

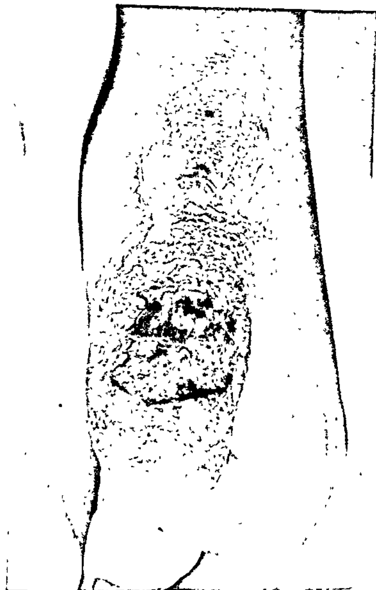


Fig 82—Primary sporotrichosis of the thumb. This is an enlargement of the thumb shown in Fig. 83.

but the other animals were apparently healthy. Meyer infected himself with a culture isolated from a horse.

Foerster reported two cases in which the disease was acquired by handling contaminated dressings from lesions of sporotrichosis, but there is no record of direct transmission of the infection from man to man.

Age, Sex, Race, and Occupation Incidence.—*In one series of 100 cases, infections were reported in children as young as 16 months and in adults 71 years of age. The average age was reported as 29 years; only ten of the patients were children* The disease occurs most often in males, especially farmers, laborers and horticulturists All races seem to be equally susceptible

SYMPTOMATOLOGY

As a result of the classical work of de Beurmann and Gougerot, the disease usually is described as conforming to one or more of six different clinical types, namely, (1) lymphatic, (2) disseminated, (3) epidermal, (4) mucosal, (5) skeletal and (6) visceral The initial lesions are found most often on one of the extremities, occurring in ninety of the 109 cases summarized by Foerster. The primary infection occurred on the hand or fingers in sixty-two of the patients, and the right hand was involved more frequently than the left

LOCALIZED LYMPHATIC SPOROTRICHOSIS is the most common form of the disease in this country. The fungus gains entry through the skin, and the first lesion may appear as early as 20 days or as long as 3 months after the inoculation. The first evidence of infection is the appearance of a hard, spherical, elastic, movable, non-tender nodule which is not adherent to the overlying skin Later, the nodule becomes attached to the skin which first assumes a pink color, then purplish and finally becomes black and necrotic Such a lesion, frequently described as a SPOROTRICHOTIC CHANCRE (Fig 82), may persist for months After a few days or weeks multiple subcutaneous nodules appear along the course of the lymphatics draining the area (Fig 83*A*.) The secondary nodules are freely movable at first, but later they become adherent to the overlying skin which gradually assumes a reddish color The nodule finally ulcerates and discharges a small amount of thin pus (Fig 83*B*) The lymphatic vessels connecting the nodules become so thickened that they are palpable as hard cords The infection may stop before the larger lymph nodes of the axilla or groin are involved When the larger lymph nodes are invaded, suppuration may or may not occur It is rare for the infection to become dissemi-



Fig. 83.—Sporotrichosis of hand and arm. *A.* Primary lesion on the thumb with chain of unruptured nodules extending up the arm. (After Vogel and Martin, Journal of Pediatrics, *17*.) *B.* Primary lesion on the thumb with ulcerated nodules extending up the arm. (After Forbus, Reaction to Injury, Baltimore, Williams and Wilkins Co.)

nated through the blood stream to other parts of the body in a patient with the localized lymphatic type of sporotrichosis. Frequently the primary lesion heals but the secondary gummatous lesions, if untreated, persist for months or years. There are remarkably few symptoms and the patient usually is afebrile.

The DISSEMINATED FORM of sporotrichosis is seen more frequently in France than in the United States. Usually, there is no detectable primary lesion. The onset is insidious and the first symptom noted is the presence of numerous hard subcutaneous nodules scattered over the body, suggesting blood stream infection. As the nodules increase in size, the overlying skin may become involved, but it is unusual for such skin lesions to ulcerate. If the lesions are incised, a thin viscid pus is obtained; but after a period of time the discharge from such lesions becomes thick and purulent. Incisions frequently are followed by the development of chronic ulcers which discharge persistently. Additional cutaneous lesions may develop from a spreading of the infection to skin adjacent to the ulcer. Foerster has described a particularly fulminating type of disseminated sporotrichosis in which the infection begins insidiously but is followed by the formation of multiple subcutaneous nodules which ulcerate rapidly to develop tuberculoid, syphiloid or ecthymiform lesions. Patients with the disseminated form of the disease are acutely ill, and frequently die in a cachectic state within a period of weeks or months.

The EPIDERMAL FORM of sporotrichosis is characterized by extensive involvement of the skin, and usually is seen in patients who have one or more nodules of either the ulcerative or the non-ulcerative type. The skin lesions are of many types and may appear as infiltrated plaques, areas of folliculitis, nodular crusted lesions, papulids and intertrigo or as weeping, fungating, verrucous or papillomatous lesions. Such lesions may simulate verrucous tuberculosis, papulonecrotic tuberculids, scrofuloderma, blastomycosis, sarcoid, papuloulcerative and crustaceous syphilids, acne and epitheliomas. Small, gummatous foci and micro-abscesses usually are found associated with such lesions. In spite of the extensive cutaneous involvement, the patients usually have but few systemic symptoms. The infection may persist for months or years, and resists all forms of non-specific local treatment.

SPOROTRICHOSIS OF THE MUCOUS MEMBRANES may occur as a primary disease or as a secondary manifestation of the disseminated form. The involved areas may be located in the nose, mouth or pharynx, and begin as erythematous, ulcerative, suppurating, vegeta-

tive or papillomatous lesions which may simulate the clinical pict[illegible] of angina, stomatitis, glossitis, laryngitis or rhinitis. The regio[illegible] lymph nodes are enlarged. False membranes occur only rarely. He[illegible]ing of the involved areas is by scar formation, but the scars are s[illegible] and pliable and there is little resultant deformity. The fungi m[illegible] persist in the lesion after apparent healing, the patient becoming [illegible] "carrier." The conjunctiva may be infected spontaneously, and in t[illegible] case reported by Wilder an accidental infection of the conjuncti[illegible] occurred in the laboratory.

SKELETAL SPOROTRICHOSIS is relatively rare, but may occur in t[illegible] absence of cutaneous lesions. Infections of the bones, joints, tend[illegible] *sheaths and muscles have been reported.*

VISCERAL SPOROTRICHOSIS is rare even if the infection is dissem[illegible]nated, but pyelonephritis, orchitis, epididymitis and mastitis due [illegible] *S. Schenckii* have been reported. In contrast to the other mycoses, t[illegible] lungs rarely are the site of the primary disease. The literature on pu[illegible]monary sporotrichosis has been analyzed critically by Forbus. W[illegible] have seen one case in a child who had a marked enlargement of th[illegible] tracheobronchial lymph nodes. *S. Schenckii* was isolated from th[illegible] sputum, and the skin test to a heat-killed vaccine made from a[illegible] autogenous culture was positive. Her serum, diluted 1:1000, cause[illegible] [illegible] of spores obtained from culture. Th[illegible]

[illegible]

MYCOLOGY

A critical examination of cultures obtained from patients wit[illegible] sporotrichosis suggests that one species, *S. Schenckii*, is the sole etiologic agent. Separation into different varieties or species has been *based on the different colors of colonies on artificial* cultivation, variations in distribution of spores on the hyphae and, in one instance, on the production of "ray-shaped" bodies in lesions. Since a culture [illegible] greatly in pigment pro[illegible] [illegible] on another) and [illegible] [illegible]ristics have little value in species differentiation. Moreover, the production of "ray-shaped" bodies in lesions has been noticed in many other fungus *infections (Actinomyces, Aspergillus, Coccidioides, Cryptococcus)* and cannot be considered a specific finding.

Direct Examination.—The fungus is supposed to appear in the pus from human lesions as small, gram-positive, cigar-shaped bodies within the polymorphonuclear cells or within giant cells. These obser-

vations are too infrequent to be of diagnostic value, and the mycologic diagnosis is dependent upon cultural studies.

Cultures.—Pus is collected from unopened subcutaneous nodules with sterile needle and syringe or is obtained from open chancre-like lesions by swabbing. Such materials should be streaked on blood agar and Sabouraud's glucose agar slants and maintained at 37° C. and room temperature respectively. On Sabouraud's glucose agar at room temperature, the growth is recognizable within 3 to 5 days At first, the colonies are small and white and there is no aerial mycelium. As growth increases, the surface of the colony becomes moist, wrinkled and membranous. The color may vary from cream to black (Fig. 84*A*, *B*); individual strains are not constant in their pigment formation and will change frequently when transferred to fresh media.

Microscopically, the delicate (2 μ in width), branching, septate hyphae bear conidia laterally or in groups from the ends of lateral branches. (Fig. 84*C*.) The conidia are pyriform, ovoid to spherical, *but become round and thick-walled in old cultures and are 2 to 4 by* 2 to 6 μ in size. Their variable distribution along the hyphae prevents separation into different species.

Animal Inoculation.—Pus should be inoculated intraperitoneally into male white rats. Such inoculated animals develop peritonitis and severe orchitis, and organisms can be seen by direct examination and cultured from these infected sites. Smears of pus from such *lesions* reveal numerous gram-positive, cigar-shaped, intracellular organisms. Such tissue forms are seen rarely in material from human lesions

Mycologic Diagnosis.—Culturing of the organisms is the best method of establishing the *diagnosis of sporotrichosis. If possible,*

trichum sp. Smith, 1898; *Sporothrix Schenckii* Hektoen and Perkins, 1900, *Sporotrichum Beurmanni* Matruchot and Ramond, 1905, *Sporotrichum asteroides* Splendore, 1909; *Sporotrichum equi* Carougeau, 1909; *Sporotrichum Jeanselmei* Brumpt and Langeron, 1910; *Sporotrichum Councilmani* Wolbach, 1917.

PATHOLOGY

In the usual case of sporotrichosis, THE CAUSATIVE ORGANISM CANNOT BE DEMONSTRATED IN SECTIONS OF TISSUE, and realization of this fact is of the greatest importance in diagnosis. Since sporotrichosis most frequently involves the upper extremities in a characteristic manner, a clinical diagnosis often can be made with certainty and corroborated by culturing the fungus. Furthermore, the less common involvement of the lower extremities or of the eye, or regions about the eye, might permit a clinical diagnosis. Less characteristic clinical appearances of sporotrichosis probably would not suggest the disease, and biopsy would be the first diagnostic procedure. Without knowledge of the need for culture, the pathologist might well make an incorrect diagnosis. Some of the atypical forms of sporotrichosis which have been described are mycetoma, solitary gummatous sporotrichosis, generalized subcutaneous ulcerating sporotrichosis or purely epidermal sporotrichosis. Sporotrichosis of the joints caused by *S Councilmani* has been reported.

Biopsy.—Biopsy findings will depend on the site from which tissue is taken. If taken from the edge of a subcutaneous abscess, the wall will show necrosis with some polymorphonuclear neutrophils and more peripherally giant cells can be found (Fig 85), together with macrophages and a chronic inflammatory reaction, often with fibrosis. Sections of sporotrichotic nodules may show central caseous necrosis without abscess formation

In the usual case, organisms cannot be seen in microscopic section, in pus or necrotic material from the lesion. Organisms may be present but in such small numbers and so isolated that they are confused with nuclear fragments from necrotic cells. In mice experimentally inoculated in the abdominal cavity or in the foot with pus from a human case of sporotrichosis, the tissue form of the organism develops in enormous numbers, both freely and within macrophages. Such tissue forms appear as gram-positive, usually small (3 to 5 μ), fusiform organisms which reproduce by budding. The mycelial form of the organism is not seen in tissue. Because of the failure to demonstrate organisms in most cases of human sporotrichosis, it is important that part of the biopsy material be planted on Sabouraud's medium.

The histologic appearances of sporotrichotic lesions may be similar to those in tuberculosis, syphilis, tularemia, plague and in fungus diseases other than sporotrichosis. In searching for the causative agent in sections, it should be borne in mind that in all the known

fungus diseases of man other than sporotrichosis, the causative fungus usually can be seen in sections stained with hematoxylin and eosin or by Gram's method.

Autopsy.—The disseminated form of sporotrichosis may result in death following widespread ulceration of the skin, but may show

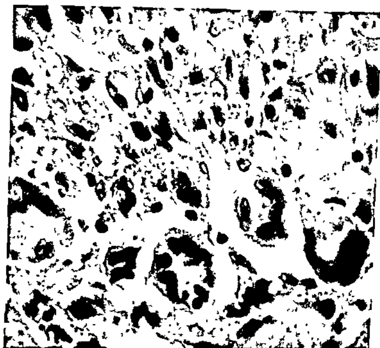


Fig 85 —Sporotrichosis Giant cell reaction at edge of sporotrichotic abscess. Note absence of fungus forms in giant cells H & E × 750

only insignificant visceral lesions. Primary infections of the lungs and of other viscera are extremely difficult to prove and occur, if at all, as great rarities.

IMMUNOLOGY

Serology.—The sera of patients with sporotrichosis contain antibodies for the fungus which can be demonstrated by the complement fixation and agglutination technics. However, the preparation of suitable spore suspensions is a tedious procedure, requiring special filtration methods to remove fragments of hyphae; large amounts of

antigen are necessary to perform a quantitative test, and there has been no attempt to standardize such antigen suspensions, making it difficult to correlate titers with clinical findings. Such technical difficulties probably explain the numerous cross-reactions obtained by the French observers, in particular, who reported that *Sporotrichum* antigens were agglutinated by sera from patients with unrelated fungus infections, including some of the dermatomycoses.

Hypersensitivity.—Patients with sporotrichosis frequently give a positive skin reaction when tested with dead *Sporotrichum* antigens. The clinical significance of such hypersensitivity has not been evaluated

DIFFERENTIAL DIAGNOSIS

The primary lymphatic form of sporotrichosis is so characteristic in its evolution that the diagnosis is obvious. In the more complicated cases, sporotrichosis should be suspected when the patient has multiple polymorphous lesions which fail to respond to ordinary methods of treatment. Cultures, preferably from unopened lesions, afford a ready method of confirming the diagnosis Agglutinations, skin tests and complement fixation tests may be done to supplement cultural methods

Sporotrichosis must be differentiated from syphilis, tuberculosis, pyogenic infections, glanders, leprosy, tularemia, coccidioidomycosis, both North American and South American blastomycosis, deep-seated trichophytosis and granulomas caused by drugs

PROGNOSIS

The prognosis usually is excellent with adequate treatment except in the fulminating disseminated form, certain of the visceral forms, in cases involving the mucous membranes of the pharynx or larynx or when the patient already is debilitated by cancer or tuberculosis

TREATMENT

Potassium iodide is practically a specific in the treatment of sporotrichosis It should be given in rapidly increasing doses, beginning with 10 drops of a saturated solution three times a day and increasing by 5 drops with each of the three daily doses until the patient is receiving as much as 30 to 40 drops three times a day. The drug should be diluted in water or milk. To avoid recurrences of the disease, iodides should be continued for 4 to 6 weeks after apparent

complete recovery. There is some indication that patients who relapse as a result of insufficient treatment may not respond so rapidly to a second course of iodides. If indigestion follows oral iodide administration, sodium iodide in daily doses of 1 Gm. may be given intravenously.

Open lesions should be washed and compressed with an aqueous IODIDE-IODINE solution containing 2 per cent potassium iodide and 0.2 per cent iodine.

X-ray therapy has been found useful as a supplementary treatment for individual lesions.

*Surgery, such as incision, excision, cautery or curettage, is contra*indicated because such procedures frequently are followed by increased suppuration and prolonged ulceration Material for cultures should be obtained by aspiration, and even large collections of pus are best evacuated by this method.

Vaccines prepared either from an autogenous or a stock culture of *S. Schenckii may be used as supplementary treatment in cases which* respond slowly to the iodides.

In the resistant pharyngeal and laryngeal types, one should suspect a secondary infection with the Vincent's type of fusospirochetal organisms. If these organisms are present, one should administer neoarsphenamine intravenously in biweekly doses of 0.3 Gm.

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Chapter XI

MADUROMYCOSIS

(*Madura Foot, Mycetoma*)

MADURA FOOT is a distinct clinical entity, presenting a uniform clinical and pathologic picture in spite of the fact that a number of different fungi can cause the disease.

Definition.—Maduromycosis is a chronic infection affecting usually the feet and rarely the hands or other parts of the body, caused by a variety of fungi belonging to different species and genera, and characterized by the development of tumefactions and sinuses

Geographic Distribution.—Maduromycosis occurs most frequently n tropical and subtropical zones where few people wear shoes and he feet come in direct contact with the soil Instan[illegible] reported from India, Africa E[illegible] Canada and the U[illegible] chusetts, [illegible] Georgia, A[illegible] alent in the [illegible] [illegible] part of the United States [illegible] The infection [illegible] Carolina, twenty-eight cases collected by Brindley and Howell were found

Source of Infection.—The source of infection is evidently exogenous, and more than one-half of the patients gave a history of an injury, such as a minor scratch, a bruise or a wound produced by a splinter. In a series of 100 cases, ninety-three occurred on the foot, two on the leg, three on the hand and two on the trunk. A case of *Aspergillus nidulans* infection of the forearm, nose, cheek and post-auricular area was reported as an instance of maduromycosis by Puestow

Of the organisms isolated from maduromycosis (Table III), most have been found to occur either as saprophytes in the soil or on plants Approximately one-half of the cases have been caused by members of the aerobic group of actinomycetes or *Nocardia* according to the terminology suggested by Henrici and Waksman and used elsewhere in this manual, this is in contrast to actinomycosis in which the anaerobic *Actinomyces bovis* is the usual etiologic agent.

TABLE III: ORGANISMS ISOLATED IN CASES OF MADUROMYCOSIS

(Modified after Gammel. The name *Actinomyces* has been retained in this table, although many authorities prefer to call the aerobic forms *Nocardia*)

I. Class: SCHIZOMYCETES

A. Genus, *Actinomyces*

1. *Actinomyces bovis* Harz, 1877
2. *Actinomyces mexicanus* Boyd and Crutchfield, 1921
3. *Actinomyces asteroides* (Eppinger) Gasperini, 1894
4. *Actinomyces bahiensis* (Pirajá da Silva) Brumpt, 1927
5. *Actinomyces convolutus* (Chalmers and Christopherson) Brumpt, 1927
6. *Actinomyces (Oospora) indicus* Kanthack, 1892
7. *Actinomyces madurae* (Vincent) Lachner-Sandoval, 1898
8. *Actinomyces somaliensis* Brumpt, 1927
9. *Actinomyces sp.* Yazbek, 1920 (Seems closely related to *Actinomyces somaliensis*)

II. Class FUNGI IMPERFECTI

A. Genus *Madurella*

1. *Madurella mycetomi* (Laveran) Brumpt, 1905
2. *Madurella Bovoi* Brumpt, 1910
3. [illegible]

F. Genus: *Cephalosporium*

1. *Cephalosporium recifei* Leão and Lobo, 1914
2. *Cephalosporium sp.* Carrión, 1940

III Class Ascomycetes

A. Genus *Allescheria*

1 *Allescheria Boydii* Shear, 1921

B Genus *Aspergillus*

1 *Aspergillus Bouffardi* Brumpt, 1906

C Genus *Sterigmatocystis*

1. *Sterigmatocystis nidulans var Nicollei* Pinoy, 1906

D Genus *Penicillium*

1 *Penicillium mycetogenum* Mantelli and Negri, 1915

Age, Sex, Race, and Occupation Incidence.—The disease is most common between the ages of 21 and 40, but may occur at any age from 12 to 80 years. The disease occurs more commonly in men than in women, ninety-two of the 100 patients in the series analyzed by Bocarro were males All races seem to be equally susceptible to this infection In Bocarro's series of 100 cases, ninety-one of the males were farmers and seven of the eight females were wives of agriculturists.

SYMPTOMATOLOGY

The mode of onset is neither characteristic nor uniform With or without a history of previous injury, the first detectable lesion may be (1) a small papule, (2) a small nodule which is deep-seated and fixed, (3) an indurated area surmounted by a vesicle, or (4) an abscess which ruptures with subsequent formation of a fistula The disease progresses slowly and is at first characterized by periods of remissions and relapses As many as six or eight papules may form in succession, or as many as twelve abscesses may develop (Fig. 86) and disappear over a period of months or years before the entire foot becomes involved and presents the characteristic clinical picture. The classical picture of swellings and deformities may develop within a period of months, but it usually takes much longer, sometimes as many as 10 to 15 years

As the infection extends deeper into the tissues, the muscles, bones, fascia and tendons may become involved and the foot or hand becomes club-shaped or may develop into a globose mass two or



Fig. 86.—Maduromycosis of the foot, caused by *Monosporium apiospermum*. Note the swelling of the foot and the multiple discharging sinuses

three times the normal size. The skin becomes discolored, and pitted scars, nodule formation and multiple sinuses develop. There is no loss of sensation in the skin. Nodules frequently develop about the openings of fistulas from which a serosanguineous or "oily" fluid, containing the diagnostic granules, is draining. The characteristic granules may be yellow, white, orchid, red or black. The yellow and red granules usually are found in infections caused by species of the genus *Actinomyces* (*Nocardia*), and the black granules are found more often in infections caused by moldlike fungi. Attempts to classify the infection according to the color of the granules have been abandoned because of unpredictable variations.

There is little SYSTEMIC REACTION unless the lesions are secondarily infected. Pain is present rarely, even when the affected part is manipulated, although localized areas of tenderness may develop in nodules before they rupture and drain. The patient generally can walk until the disease has progressed to the stage where there is marked wasting of the leg muscles.

In the terminal stages of the disease, secondary infection with pyogenic cocci occurs, and the patient dies after a variable period of time in which fever, malaise and prostration are prominent symptoms.

X-rays.—Films of the affected parts usually show involvement of the small bones of the feet or hands (Fig. 87) and both destructive and proliferative reactions are seen. In general, the actinomycetes (*Nocardia*) produce more bone destruction than do the other types of infecting fungi.

Laboratory Examination.—There is nothing characteristic about the blood picture in the early stages of the disease. In late stages with severe secondary infection, the patients have a leukocytosis with an increase in the neutrophils.

MYCOLOGY

The numerous fungi that have been isolated from cases of maduromycosis fall into three classes, SCHIZOMYCETES, ASCOMYCETES and FUNGI IMPERFECTI. In the group of Schizomycetes, several species of the genus *Nocardia* are represented, in the Ascomycetes are found the genera *Allescheria*, *Aspergillus* and *Penicillium*, and in the Fungi Imperfecti are found species of the genera *Madurella*, *Indiella*, *Cephalosporium*, *Monosporium* and *Glenospora*. There is little doubt that many of the *Nocardia* are identical and that a number of the



Fig 87 —Maduromycosis X-ray of foot shown in Fig. 86. Note the destructive lesions in phalangeal and metatarsal bones

described species can be reduced to synonymy by careful studies. It has been shown recently by Emmons that *Monosporium apiospermum* is the imperfect conidial stage of *Allescheria Boydii*. In Table III is a list of the various fungi which have been isolated from cases of maduromycosis; this was compiled by adding a few to the list collected by Gammel. An attempt to group the fungi by the character of pigmentation of the "grain" has been abandoned because of the variety of cultures obtained when grains of the same color were cultured.

Direct Examination.—Pus should be obtained from the multiple draining fistulas or aspirated from unopened fluctuant areas with a sterile needle and syringe. Material obtained by curettage or biopsy should be collected in a sterile petri dish. Pus, curettings or biopsy tissues should be examined grossly for "grains" which are seen as small (0.5 to 2 mm), oval, irregularly shaped masses which may be white, yellow, red or black in color. Such grains should be examined microscopically after placing them in a drop of water or 10 per cent potassium hydroxide. The grains found in maduromycosis caused by the actinomycetes or *Nocardia* are indistinguishable microscopically from those seen in fresh preparations of material from actinomycosis. (See Fig. 7*B*) In cases of maduromycosis caused by the higher fungi, the grain is found to be composed of a central mass of segmented, branched hyphae, 2 to 4 μ in diameter, and throughout the granule are seen many large chlamydospores or hyphal swellings. (Fig. 88*B*.) Around the periphery the hyphae assume a radiating appearance, terminating in chlamydospores.

Cultures.—Material aspirated from unopened lesions should be cultured directly on Sabouraud's glucose agar at room temperature. Grains obtained from open, draining fistulae should be washed in [illegible]

logic agents, *Monosporium aspiospermum*, is described in detail.

M. apiospermum is a rapidly growing fungus producing a white, cottony aerial mycelium which later turns gray or becomes buff to brown in color (Fig 89*A*) Microscopically, ovoid and pyriform conidia, 8 to 10 μ long by 5 to 7 μ wide, are produced singly at the ends of long conidiophores or from the sides of the mycelium on short conidiophores (Fig. 89*B*) Tufts of conidiophores (coremia), each bearing a single conidium at the tip, are seen occasionally, as

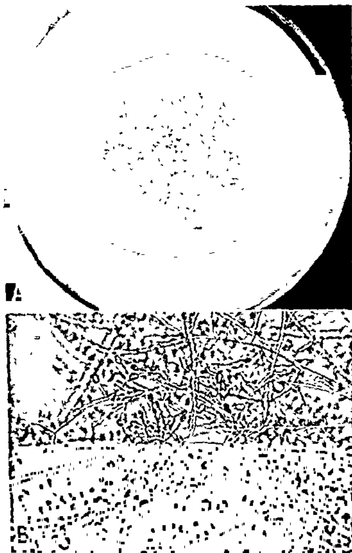


Fig. 89.—*A* *Monosporium apiospermum* on Sabouraud's glucose agar, twenty days, at room temperature *B* *Monosporium apiospermum*, from Sabouraud's glucose agar Note the single conidia on the ends of the conidiophores × 305.

are conidiophores which sometimes branch and produce a whorl of sterigmata, each terminating in a conidium. Sclerotium-like bodies may or may not be present in the cultures. In a study of one strain, Emmons was able to show that the sclerotium-like structures developed into fertile ascocarps which produced asci and ascospores of the type found in *Allescheria Boydii*, an ascomycete isolated from Madura foot. *M. apiospermum* is, therefore, the imperfect stage of *A. Boydii*.

Animal Inoculation.—There is no suitable laboratory animal in which a type of disease similar to that seen in humans can be produced. Introduction of pure cultures of *M. apiospermum* into the knee joints or feet of animals results in pathologic reactions similar to those seen in man, but the lesions are not progressive.

Mycologic Diagnosis.—The grains of *M. apiospermum* are seen as oval or irregular masses, white, yellow, red or black in color in the pus from draining fistulae, curettings or biopsied tissue. Microscopically, they are distinguished from *Actinomyces* granules in that the hyphae are broad, 2 to 4 μ in diameter, and contain numerous chlamydospores, particularly at the periphery of the grain.

Monosporium apiospermum Saccardo, 1911. Synonymy.—*Scedosporium apiospermum* Saccardo, 1914; *Glenospora Clapieri* Catanei, 1927; *Indiella americana*, Delamare and Gatti, 1929.

PATHOLOGY

Maduromycosis is so similar to actinomycosis of the extremities that the pathologic description applies to both diseases, and regardless of the variety of causative organisms, the gross and microscopic picture is, in general, the same.

Biopsy.—If the affected extremity is amputated, it should be embalmed or perfused with solution of formaldehyde to prevent excessive wrinkling of the skin and the specimen should be sawed sagittally. The changes consist of numerous small abscesses and sinuses in the subcutaneous tissues which ramify along tendons, often reach into [illegible] extend to the surface [illegible] or granules of the fungus usually can be seen on the cut surface of the tissues, *sometimes in considerable numbers*, especially in the abscesses and sinuses. When the granules are black, they stand out sharply as minute specks, one to several millimeters in diameter

The degree of suppuration and fibrosis varies from specimen to specimen and from place to place in the same specimen. The osteomyelitis is predominantly destructive without formation of new bone. With the production of much fibrous tissue, elephantiasis may result. Healing may be so complete in some areas that only dense scars, [illegible] neoplasm.

Microscopically, the fungus grain is seen to be surrounded by pus or, in some instances, by macrophages or giant cells. (Fig. 88*A*.) More peripherally, the chronic inflammatory cells may be lymphocytes, plasma cells, eosinophils or macrophages. Massive accumulations of lipoid-laden macrophages may occur and account for the bright yellow color noted grossly in some tissues. If the fibrosis about the grain is marked, the appearance is much like that of a tubercle.

While the grains are demonstrated well in sections stained by hematoxylin and eosin, they should be stained regularly by the method of Gram, as advised in the chapter on actinomycosis. The gram-stained preparation aids in differentiating bacterial masses from fungus grains. It also shows the branching of the mycelium in actino- [illegible] fast when decolorization is carried out by the usual acid-alcohol method. [illegible] mentation.

IMMUNOLOGY

No useful procedures have been developed for the serologic diagnosis of maduromycosis.

DIFFERENTIAL DIAGNOSIS

The diagnosis is simple when once the possibility of maduromycosis is considered. The characteristic "grains" may be demonstrated in the fresh discharges, in fluid from fistulous tracts or in biopsied material from the wall of an abscess. The "grains" may be seen with the naked eye, but should be studied with the microscope, unstained, in wet preparations or in preparations cleared with 10 to 20 per cent sodium hydroxide.

Maduromycosis must be differentiated from tuberculosis, syphilis, neoplasms, elephantiasis, coccidioidomycosis, blastomycosis, yaws, sporotrichosis and paramycetoma. The paramycetomas are characterized by a total absence of "grains" in the discharges and in the affected tissues. The causative organism is usually a member of the actinomycetes which does not produce definite granules.

PROGNOSIS

Maduromycosis rarely heals spontaneously. The disease continues to progress, and the patient eventually dies of secondary infection if the disease process is not eradicated by excision or amputation. The cases caused by the moldlike fungi usually develop more slowly and are less prone to secondary infection than those caused by the actinomycetes.

TREATMENT

Potassium iodide, copper sulfate and various other fungicidal drugs have been used without success Local excision may be effective in relatively early and localized lesions; it is important to remember that the disease process in the underlying tissues is generally much more extensive than is suggested by the superficial lesion, and excision should include a wide zone of apparently healthy tissue Cauterization is of little value.

Before the introduction of sulfonamides, amputation was the only satisfactory treatment for the advanced cases Excellent results usually were obtained if the operation was performed before the patient was moribund from secondary infection.

Dickson, in 1941, reported the cure with sulfanilamide of a case of maduromycosis of the foot of 15 years' duration, caused by one of the ACTINOMYCETES (*Nocardia*). There was extensive bone destruction, as shown by the x-rays. The

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Chapter XII

ASPERGILLOSIS

ASPERGILLI are the most common and most troublesome fungus contaminants that are encountered in the laboratory. Some species are undoubtedly pathogenic and can produce lesions in the tissues of man and animals

Definition.—Aspergillosis, caused by certain species of *Aspergillus*, is characterized by the presence of inflammatory granulomatous lesions in the skin, external ear, nasal sinuses, orbit, bronchi or lungs and occasionally in the bones and meninges

Geographic Distribution.—Aspergillosis is found in all parts of the world Although the first necropsy was done by Virchow in 1856, most of the early instances were reported from France. Since the beginning of the twentieth century gradually increasing numbers of case reports have appeared in Germany, England, Italy, Australia and North and South America.

Local infections are particularly common in the tropics. Reeh found 215 cases of ear infections in the Panama Canal Zone within a period of several months.

Source of Infection.—Aspergilli are ubiquitous in nature. Many species are pathogenic for plants; some infect insects, birds and domestic animals. Birds are particularly susceptible and 40 per cent of the necropsies on penguins showed evidence of infection with *Aspergillus*.

Age, Sex, Race, and Occupation Incidence.—Adults are infected more frequently than children, and the disease occurs in males more often than it does in females. The disease has been found in all races. Infection occurs most often in those who are exposed frequently to massive doses of fungus spores, as in (1) squab feeders who take the grain into their mouths to moisten it and incidentally inhale clouds of spores; (2) fur cleaners who use rye flour, containing spores, as grease removers; and (3) agricultural workers exposed to the dust from threshers

SYMPTOMATOLOGY

The symptoms vary with the location of the infection, whether in the ears, sinuses, orbit, skin, bones, vagina, bronchi or lungs.

The EAR is the most common site of infection and is discussed in the chapter on otomycosis.

A case of NASAL and MAXILLARY SINUS INFECTION was reported by Kelly. The symptoms were those of a pyogenic sinus infection except [illegible]

[illegible] lary and sphenoid sinuses were infected with subsequent extension into the orbit. Rosenvald studied a case in which both dacryocystitis and blepharitis were present.

GENITAL LESIONS are rare but have been reported in both sexes by Castellani. In Goldstine's case of *A fumigatus* vaginitis, the symptoms were those of chronic leukorrhea and a biopsy of a grayish nodule showed the organism in the necrotic tissue

Several species of Aspergillus have been isolated from patients with maduromycosis *Link reported a fatal meningeal* infection due to *Aspergillus*, and Shaw and Warthen studied a case with involvement of the vertebrae and ribs Meyers and Dunn reported an instance of chronic granulomatous *Aspergillus* infection of the hand.

and were able to produce nodular, ulcerating lesions in guinea pigs inoculated with the cultures isolated from the patient.

Aspergilli frequently are isolated from the sputum of patients with chronic bronchitis and intrinsic asthma, but it is difficult to prove the relationship of the fungus to the disease process; in most instances, it proves to be an accidental contaminant or merely a secondary invader.

Primary pulmonary aspergillosis is rare and difficult to diagnose until necropsy The symptoms are similar to those of pulmonary tuberculosis with cough and mucoid or mucopurulent sputum which frequently contains blood. In some cases, the general health of the patient is not affected, but in others there is a remittent fever, loss of weight, obvious toxemia and the patient slowly becomes cachectic and dies The physical findings are indistinguishable from those of chronic pulmonary tuberculosis

X-rays.—Smooth, dense lesions may be present in the lungs (Fig 90) and cavity formation is frequent Less commonly, the lesions are nodular and diffuse

MYCOLOGY

Species of *Aspergillus* are the most common laboratory contaminants, and are found frequently in Sabouraud's slants inoculated with materials such as sputum, skin scrapings, and so on Even the finding of aspergilli repeatedly in cultures of such material cannot be considered as conclusive evidence that the fungus is the primary etiologic agent since it may represent a superimposed infection. *A fumigatus* is the species most often associated with disease processes

Direct Examination.—Sputum should be pressed to a thin film under a cover glass and examined microscopically The fungus appears as broken fragments of hyphae with numerous small (2 to 3 μ), round, dark green spores scattered throughout the preparation.

Cultures.—Suspected materials should be cultured on Sabouraud's glucose agar slants and maintained at room temperature. The colonies are fast growing and appear first as white, filamentous growths on the surface of the medium, but they quickly become green to dark green in color as spores are produced (Fig 133) Microscopically, all species of *Aspergillus* are characterized by conidiophores which expand into large vesicles at the end, the surfaces of which are covered with sterigmata bearing long chains of spores The characteristic spore heads are seen best by laying the culture tube on the stage of the microscope and examining the edge of the slant with the low power objective In such undisturbed preparations, the long chains

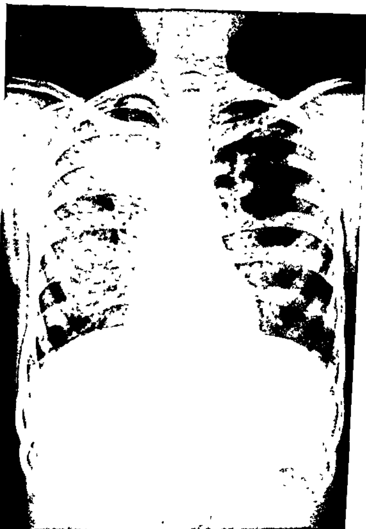


Fig. 90.—Aspergillosis of the lungs, proved by repeated demonstration of hyphal elements in the fresh sputum The patient gave an immediate wheal-like reaction to a vaccine made from his own culture (Courtesy of Dr H A Bray New York State Hospital for Incipient Tuberculosis, Ray Brook, N Y)

of spores may be seen. Microscopic preparations should be made by teasing a bit of the aerial growth in a drop of mounting fluid, such as lactophenol cotton blue, and examining the preparation under a cover glass. The typical swollen conidiophore bearing the sterigmata can be identified, but usually the long, fragile spore chains are broken and only a few spores will remain attached to the sterigmata. For species identification, it is necessary to refer to the keys found in Thom and Church's monograph.

Mycologic Diagnosis.—The diagnosis is based on finding mycelial fragments and numerous spores on direct examination and on obtaining a culture showing the typical conidiophore and spore chains of *Aspergilius* Since aspergilli are fast growing and often are contaminants, their growth may hide or completely inhibit the growth of a slower-growing true pathogenic fungus which may have been overlooked in the clinical material.

PATHOLOGY

Biopsy.—The growth of the fungus in the ear canal or vagina may be limited to the layer of necrotic, keratinizing, stratified, squamous epithelium and excite little or no inflammatory response

In the case of aspergillosis of the orbit described by Wright, sections of the tissue showed giant cells containing septate mycelial filaments Polymorphonuclear cells and macrophages also were present The filaments in giant cells were not seen readily with hematoxylin and eosin stain, but were demonstrated in Leishman's stain. Fructification occurred in cultures of the organism but was not found in the tissues

Autopsy.—In many of the cases reported as aspergillosis of the lungs and bronchi which were studied at autopsy, the question has been raised as to whether the *Aspergillus* was a primary or secondary invader For example, aspergilli can be found growing on the walls of a tuberculous cavity Similar difficulties arise in evaluating the finding of *Aspergillus* in pulmonary abscesses

Aspergillosis of the lungs presents a variety of appearances which vary from abscesses to scattered grayish-yellow nodules. Cavity formation in primary pulmonary aspergillosis apparently is not common.

The mycelial growth in pulmonary aspergillosis usually is not associated with fructification so that confusion with mucormycosis occurs In both diseases, necrosis is the chief change in the tissues but inflammatory cells may be present, and, in some instances, a chronic inflammatory reaction with giant cells is seen

In Linck's case of fatal aspergillosis of the meninges, tubercle-like structures occurred at the base of the brain and there was a polymorphonuclear reaction without chronic inflammation. In Just's case of cerebral abscess, there was purulent destruction of the bony roof of the orbit and a connection with the frontal sinus, the sinus being filled with pieces of sequestrum bathed in pus. In both cases, mycelial elements were present in the lesions and the diagnosis of aspergillosis was highly probable but not proved.

IMMUNOLOGY

Serology.—Nothing is known concerning the antibody response to *Aspergillus* infections in humans. A thermolabile hemolytic endotoxin has been extracted in Henrici's laboratory from cultures of *A. fumigatus*. Injection of the endotoxin produced swelling and necrosis in laboratory animals and caused paralysis in guinea pigs. Antibodies to the toxin could be developed in rabbits, and the antitoxin was capable of neutralizing the hemolytic action of the toxin and of passively protecting guinea pigs and mice against the effects of toxin injections.

Hypersensitivity.—Positive skin tests to vaccines and extracts have been reported, but are not indicative of actual infection of the tissues by the fungus since the patient may be hypersensitive to the fungus due to intrinsic asthma or other allergic conditions

DIFFERENTIAL DIAGNOSIS

The diagnosis of bronchial or pulmonary aspergillosis cannot be made without repeated demonstrations of branching hyphae in the sputum. The demonstration only of spores or cultivation of the fungus is not sufficient. In other lesions, biopsies are necessary and one must find the organism invading the tissues Since pulmonary aspergillosis occurs not infrequently as a secondary infection in tuberculosis, bronchiectasis and carcinoma of the lungs, these conditions [illegible] of primary pulmonary asper- [illegible]

The name [illegible] viduals for the type of miliary calcification described by Sayers and Meriwether and found by the hundreds in the Midwest of the United States in farmers and laborers who had worked in the *Aspergillus*-laden dust around wheat threshers

PROGNOSIS

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TREATMENT

The treatment of *Aspergillus* infections of the ear is discussed in the chapter on otomycosis. Pulmonary aspergillosis may be treated by either the SLOW or the RAPID method of iodide therapy, as described in the chapter on blastomycosis (p. 48). If the patient is allergic to his own organisms, he should be desensitized before the administration of iodides, as described in the chapter on blastomycosis.

Localized abscesses should be drained and granulomatous areas excised if possible. Iodide therapy should be employed after the surgical procedures. Amputation is the treatment of choice in advanced maduromycosis caused by *Aspergillus*. The earlier cases may respond to drainage and iodide therapy.

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Chapter XIII

PENICILLIOSIS

There are several reports indicating that fungi of the genus *Penicillium* can cause infection in the lungs. Pulmonary infections have been reported by Talice and MacKinnon, Nussbaum and Benedek, and Aime, Creuze and Kresser. The case reported by Aime *et al.* presented the clinical and x-ray characteristics of pulmonary abscess. Species of *Penicillium* often are found in otomycosis. (See Chapter XXII, p. 279.)

Mycology.—The number of species of *Penicillium* is so large and the mycologic data on species pathogenic for man are so small that it is not worthwhile to include a detailed description here. On DIRECT EXAMINATION, small, round spores and bits of hyphae, similar to those seen in aspergillosis, should be found. On CULTURE, species of *Penicillium* grow at a comparatively fast rate and may develop a variety of colors The characteristic microscopic features of cultures of *Penicillium* are included in the section on contaminants. (Fig. 139.) For species identification, it is necessary to refer to Thom's monograph.

Diagnosis.—Species of *Penicillium*, like species of *Aspergillus*, are present so constantly in the air and in the laboratory that it is exceedingly difficult to establish the etiologic relationship even when found in sputum or other secretions.

Treatment.—Little specific information is available as to the best method of therapy. Presumably, the treatment should be the same as that recommended for aspergillosis (p. 197).

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Chapter XIV

MUCORMYCOSIS

Certain species of *Mucor* produce epidemics of paronychia in orange workers, and occasionally pure cultures of *Mucor* are found in cases of otomycosis

Several cases of pulmonary mucormycosis have been reported, the first in the human was studied by Paltauf in 1885. The primary infection was in the lungs, but metastatic abscesses developed in various organs before death Ernst reviewed the literature in 1918 and reported an additional case from this country Recently, Gregory, Golden and Haymaker have reported three instances of brain and meningeal infection, presumably due to species of *Mucor* although cultures were not obtained.

Mycology.—The microscopic characteristics of the genus *Mucor* are described in the section on contaminants (Fig 148.)

Diagnosis.—*Mucor*, like *Aspergillus* and *Penicillium*, is a common laboratory contaminant It may be a secondary invader but only rarely is it a primary invader The diagnosis of mucormycosis should be made reluctantly and only when the evidence is overwhelming

Treatment.—The treatment for mucormycosis is the same as for aspergillosis

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Chapter XV

RHINOSPORIDIOSIS

ALTHOUGH the etiologic agent of rhinosporidiosis has not been cultured, it is assumed by most observers that it is a fungus because of the morphologic characteristics of the organism as it appears in tissue.

Definition.—Rhinosporidiosis, caused by *Rhinosporidium Seeberi*, is an infection of the mucous membranes of the nose, eyes, ears, larynx and occasionally the vagina, penis and skin which is characterized by the development of friable, sessile or pedunculated polyps

Geographic Distribution.—The infection has been found in India, Ceylon, the United States, Argentina, Paraguay, Brazil, South Africa, [illegible]

area in India in a period of 18 months, and Karunaratne collected 104 instances in Ceylon.

Source of Infection.—*The organism causing this infection has not* been cultured and has not been transmitted to man or animals by experimental inoculation The disease occurs spontaneously in horses, cows and mules. Wright suggested that the infection was carried by dust or water, and Mandlick, in India, noted a high incidence *of the infection (20 per cent) in a group of workers engaged in* removing sand from the bed of a stagnant river. The disease developed only in those who dived or swam in the water It has been sug- [illegible]

velop at any age between 5 and 84 years, but is seen most [illegible] in children and young adults. Males are more often infected than females. All of the thirteen patients reported from the United States and 203 of the 231 case reports summarized by Karunaratne were men. All races appear to be susceptible to the disease. The sand divers of India are infected frequently, as are other individuals who habitually dive and swim in stagnant water

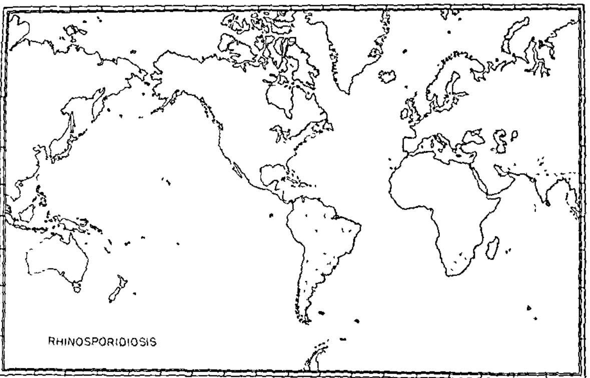


Fig. 91 – Geographic distribution of rhinosporidiosis.

SYMPTOMATOLOGY

An excellent clinical description of rhinosporidiosis has been published by Allen and Dave. The symptomatology varies according to the site of infection and the size of the tumor masses which develop.

The NOSE is the most common site of infection, occurring in 72 per cent of the 280 patients in Karunaratne's series. The first symptom usually is that of a painless itching sensation in the nose and is accompanied by the development of a profuse mucoid discharge. Purulent discharges are infrequent and bleeding is rare unless the lesion is traumatized by a blow or by scratching. The lesions at first are sessile on the mucosa, but as the tumor masses develop they become pedunculated by constriction at the base. The fully developed swellings are globoid or polypoid and those on the anterior part of the nose may hang down over the upper lip. (Fig 92.) If the growth develops in the posterior nares, it may project into the posterior pharynx where it is seen as a papillomatous tumor with or without mucinous bags. Such tumors may weigh as much as 20 Gm. The friable portions bleed easily when traumatized. The color of the lesions is distinctive and varies from pale pink to deep purplish-red. By careful inspection of the entire surface, multiple minute white spots (sporangia) usually can be seen The surface of the tumor is covered with sticky mucus and may show papillary projections, giving it the appearance of a raspberry or strawberry; older lesions may become so corrugated as to resemble a cauliflower.

In the posterior PHARYNX and in the LARYNX, the gradually enlarging polyps may produce nasal obstruction, dyspnea and dysphagia; such lesions usually are secondary to nasal involvement, but the nasopharynx only was involved in six of Karunaratne's 280 cases.

The disease was limited to the EYE in forty (14 per cent) of the cases reported by Karunaratne Small lesions developing in the conjunctivae may cause no symptoms and often are not detected by the patient. Larger growths cause symptoms similar to those produced by foreign bodies and may be accompanied by photophobia, lacrimation and injection of the conjunctiva. Conjunctival lesions in the early stages are small, pale pink, flattened, granular nodules which

tumor growth



Fig 92 —Rhinosporidiosis of nose and face The tumor mass extending down over the mouth originated in the nose (After Allen and Dave, The Indian Medical Gazette, 71)

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mation and injection of the [illegible]
early stages are small, pale [illegible]
are freely movable; later, they develop a deeper, almost splenic color and may be lobulated. (Fig. 93.) The bulbar, as well as the palpebral, conjunctiva may be affected. *The lids may be everted by excessive* tumor growth.



Fig. 92.—Rhinosporidiosis of nose and face. The tumor mass extending down over the mouth originated in the nose. (After Allen and Dave, The Indian Medical Gazette, 71.)

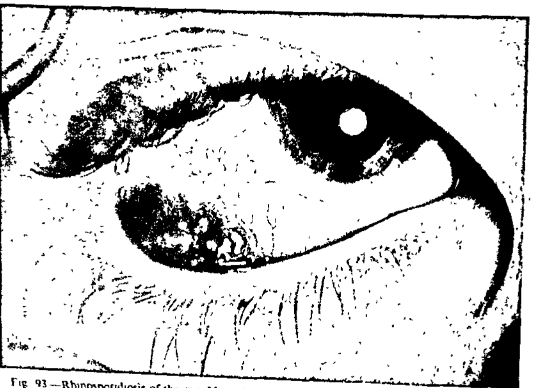


Fig. 93.—Rhinosporidiosis of the eye. Note the white spots in the lesion. The organisms are found in abundance in these areas. The tumor mass was the color of the spleen. (After Arnold and Whildin, American Journal of Ophthalmology, 25.)

Infection of the LACRIMAL SAC may block the duct and result in excessive lacrimation. The sac feels boggy, cannot be flattened and often resembles a mucocele.

The SKIN lesions begin as tiny papillomas which are elevated only slightly above the surrounding healthy surface. As they increase in size, the surface becomes crenated or warty, the tumors become pedunculated and collections of myxomatous material develop in the lesions. Early wart-like lesions are not painful unless situated on the soles of the feet; larger tumors may be painful and cause distress because of their size and weight.

Lesions of the EAR resemble ordinary aural polyps and cause no symptoms except those due to pressure Early PENILE lesions resemble venereal warts which slowly change into cauliflower-like growths Infections in the VAGINA and RECTUM resemble condylomata, hemorrhoids or rectal polyps The general health of the patient is not affected by local tumors, and the lesions may persist for as long as 35 years.

MYCOLOGY

Although the fungus has not been cultured, the life cycle of the organism in tissue, as described by Ashworth and others, can be summarized as follows·

The infecting spore is a small (6 to 7 μ in diameter), round body with a somewhat thickened chitinous wall, a nucleus and a karysome which increases in size until it becomes 50 to 60 μ in diameter and nuclear division occurs, revealing 4 chromosomes. Further increase in size and repeated nuclear divisions take place until the spore becomes 100 μ in diameter, at which time a thick layer of cellulose is deposited inside the chitinous outer membrane At one point on the periphery, however, a thinning of the wall occurs and the resulting "pore" remains until the sporangium is mature Further nuclear divisions with cleavage and rounding up of the cytoplasm eventually result in a sporangium containing approximately 4000 spores Two more divisions increase the number of spores to approximately 16,000 Such spores are spherical, 7 to 9 μ in diameter, have a thin chitinous membrane and contain a nucleus with karysome and several uniformly sized granules or spherules Such small granules, about 1 5 μ in diameter, are not thought to be reproductive bodies As the spores mature, the sporangium becomes larger (200 to 300 μ in diameter) and the spores are liberated by rupture of the sporangium at the "pore" Many investigators believe that these spores can infect tissue directly and repeat the life cycle of the fungus i* ... er

no one has been able to transmit the infection from spontaneously infected man or animals to other animals.

Direct Examination.—Direct examination of material from the polypoid masses reveals sporangia and spores. Such material may be



Fig. 94.—Rhinosporidiosis, from nasal polyp. Very large sporangium containing exceedingly numerous spores of varying sizes. Additional spores free in crevice of polyp. Immature spores elsewhere in tissue which shows chronic inflammation. H. & E. × 175.

squeezed gently with a forceps in a drop of water and examined directly under a cover glass. The exudate which adheres to the blades of the forceps also may be used, as can materials from nasal secretions. Round to ovoid spores, 7 to 9 μ in diameter, and spore-filled

sporangia should be seen in such preparations Additional smears should be made and stained by a Romanowsky's stain.

Mycologic Diagnosis.—The finding of characteristic large sporangia in polypoid masses is diagnostic The large, round thick-walled, endospore-filled structures found in coccidioidomycosis are much smaller (80 μ in diameter); the spores are smaller (2.5 μ in diameter) and they do not contain the numerous uniformly sized granules seen in spores of *R Seeberi*.

Rhinosporidium Seeberi (Wernicke) Seeber, 1912. **Synonymy.**—*Coccidium Seeberi* Wernicke, 1900, *Rhinosporidium Kinealyi* Minchin and Fanthum, 1905.

PATHOLOGY

Biopsy.—On gross examination, the polyps resulting from *R. Seeberi* are soft and nodular. Beneath the free surface of such nodules are found opaque, grayish-white flecks, representing the large sporangia On the cut surface more of the sporangia are noted, the largest usually lying just beneath the covering epithelium Lesions removed from the conjunctiva are soft, reddish, slightly irregular masses and the minute opaque points are seen (Fig 93.)

Microscopically, sporangia (up to 300 μ in diameter) filled with innumerable spores can be seen in sections stained with hematoxylin and eosin. (Fig. 94.) Ruptured sporangia also are present and endospores are scattered about on the epithelial surface or throughout the tissues. In addition, empty sporangia may be identified by their hyaline or laminated walls. Spores, as small as red blood cells, also occur in tissues, sometimes in enormous numbers Immature forms in various stages of development and small forms with a single nucleus can sometimes be seen

When liberated from the sporangium into the tissues, the spores may incite a polymorphonuclear inflammatory reaction and abscess formation and tissue necrosis may be present However, the most common reaction is that of chronic inflammation, with plasma cells and lymphocytes being most conspicuous Giant cell reaction about empty sporangial shells may occur. Vascular granulation tissue and scarring may be prominent.

Autopsy.—Cases showing generalized or visceral infection with this organism apparently have not been recorded.

DIFFERENTIAL DIAGNOSIS

The diagnosis of rhinosporidiosis is suggested by the finding on a mucous surface, especially of the nose or eye, of papillomatous or

villous polyps which are composed chiefly of friable pink or red

easily by direct examination of material for the characteristic sporangia.

PROGNOSIS

Rhinosporidiosis rarely is fatal. The lesions are uncomfortable and unsightly, but cause no difficulty except in instances where they are so large as to cause obstruction to the larynx or esophagus or where unskillful attempts at removal are followed by a fatal secondary infection with bacteria. Allen and Dave state that the smaller lesions may disappear spontaneously after 8 or 9 years.

TREATMENT

The superficial early lesions can be removed completely by careful dissection. Wright has emphasized that polyps should not be removed by a snare because of the danger of spreading the infection locally and of introducing bacteria into the wound. In advanced cases, extensive surgery supplemented by cauterization may be necessary. The TRIVALENT ANTIMONY preparations, fuadin, sulfostab (Boots), casbis (Bayer), entodon (Bayer), paranitrophenol and urea stibamine have been tried without success. There was some evidence in Allen and Dave's series that the PENTAVALENT ANTIMONY compound, neostibosan (Bayer), was helpful as an adjunct to surgical measures; the drug was given intravenously in doses of 0.3 Gm. every day or every other day until a total dose of 2 to 4 Gm. was administered.

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Chapter XVI

SYMPTOMATOLOGY, PROGNOSIS AND TREATMENT OF THE DERMATOMYCOSES

The term "dermatomycoses" refers to certain fungus infections of the skin caused by members of a well-defined group of fungi, the dermatophytes. Fungi of the dermatophyte group can invade only the superficial skin, in contrast to the organisms causing the systemic mycoses which can infect not only the skin but also the subcutaneous tissues, lungs, bones and other organs of the body As in the systemic mycotic infections, hypersensitivity plays an important role in the pathogenesis of the disease, but the allergic phenomena are confined largely to the cutaneous tissues.

A classification of the dermatophytoses on an etiologic basis is unsatisfactory because a single species of a dermatophyte can cause a [illegible]

part of the body infected; the mycologic aspects are emphasized only when prognosis or treatment must be modified, depending upon the nature of the fungus producing the lesion

A simple dermatologic formulary, giving the prescriptions for the various medications recommended for treatment, will be found in the appendix

TINEA PEDIS

(Dermatophytosis, Epidermatophytosis, Dermatomycosis, "Athlete's Foot," Ringworm of the Feet)

Definition.—Tinea pedis is a fungus infection of the feet, invading particularly the toe webs and soles, caused by *Epidermophyton floc-*

cosum, various species of *Trichophyton* and, rarely, species of *Microsporum*.

Geographic Distribution.—Tinea pedis occurs all over the world, but is more common in tropical and temperate climates.



Fig 95 —Chronic dry hyperkeratotic tinea pedis

Symptomatology.—Tinea pedis comprises such a variety of clinical types and combinations that only the commonest lesions will be described.

The CHRONIC PAPULOSQUAMOUS HYPERKERATOTIC TYPE is characterized, as a rule, by the absence of vesicles and pustules. The eruption most often is limited to the heels, soles and sides of the feet (Fig. 95) but may occur on the dorsum. The scales appear furfuraceous



Fig 96—Chronic intertriginous type of tinea pedis showing maceration and fissure between fourth and fifth toes

and branny and occur on an erythematous, thickened, patchy base which usually is well demarcated but may involve the entire sole Hyperkeratotic plaques often develop over the heel and ball of the foot, frequently in a symmetrical fashion Such lesions rarely cause symptoms and may not be noticed by the patient

A CHRONIC INTERTRIGINOUS FORM is seen in which the only clinical manifestation may be a fissure in the toe webs, usually between the fourth and fifth toes, but more commonly the epidermis in the interspaces appears white, macerated and soggy; hyperhidrosis is common



Fig. 97 —Acute eroded ulcerative pustular tinea pedis with edema and lymphangitis

and the lesions are often odoriferous. (Fig 96) Removal of the soggy epidermis exposes an erythematous, moist, red base The so-called "soft corns" often are dermatophytic in nature, and the infection tends to be dormant, representing a "carrier stage"

A SUBACUTE TYPE of tinea pedis is characterized by the appearance of vesicles or vesicopustules extending from the intertriginous area up over the toes and feet, or the soles of the feet may be involved by spreading from patches of vesicles and vesicopustules. Isolated vesicles or bullae may be present or the eruption may appear in patches, and rupture of these tense pruritic vesicles yields a clear, sticky fluid unless secondary infection has occurred. Cellulitis, lymphangitis and lymphadenitis may result from extension of this subacute process; at times the spread may resemble erysipelas.

An ACUTE FORM of tinea pedis may develop by erysipelatous spread of an eczematoid vesiculopustular nature, but more often this type of lesion is caused by secondary pyogenic infection of the vesicles and bullae. (Fig. 97.) Such vesicles and bullae contain cloudy or frankly purulent material and may result in ulceration. Such ulcerations may be so fulminating that the entire [illegible] of the foot may be undermined rapidly and [illegible] and lymphadenitis with sever[illegible] The acute lesions are edema[illegible]ous. Men are affected more often than wom[illegible], and the disease is more common in hot weather or under any condition which predisposes to hyperhidrosis or maceration of the feet. Circulatory instability, vascular stasis of the extremity, ill-fitting heavy shoes or infrequent change in socks or shoes predispose to infection.

Repeated exposure to fungi and other varieties of organisms in showers, locker rooms, and so on, may result in infection of individuals who previously have been resistant to strains of the fungus they are carrying or to those to which they are commonly exposed. Some individuals are resistant to the infection regardless of the amount of exposure. The hands may be affected and show all the types of eruption described above (Fig. 98.)

Differential Diagnosis.—The diagnosis is suggested by the presence of branny, furfuraceous, scaly patches or patches of vesicles or vesicopustules over the soles, fissures or macerative soggy epidermis in the toe webs or hyperkeratotic plaques over the heels or balls of the feet. Similar lesions may be caused by *Candida albicans* (Fig. 99.)

Tinea pedis must be differentiated from contact dermatitis, pustular psoriasis, acrodermatitis perstans, dermatitis repens, pustular bacterids, pyodermas, dyshidrosis, moniliasis, hyperhidrosis, secondary syphilis, arsenical keratoses and drug eruptions, which can be excluded by the demonstration of the fungus in the skin.

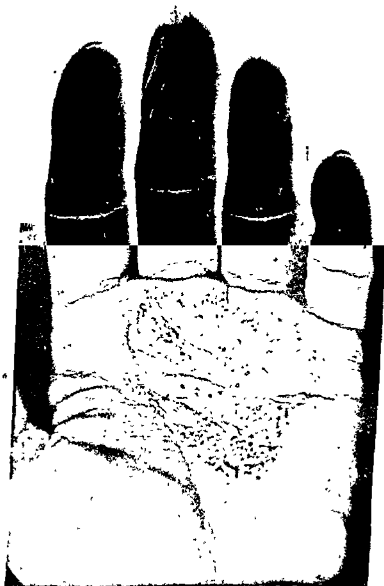


Fig 98.—Chronic vesi tular dermatop lm.

Prognosis.—Tinea pedis, as a rule, is cured readily unless the offending organism is *T. rubrum* which is extremely difficult to eradicate. Re-infection, rather than relapse, is common if there are repeated exposures to infected shoes, floors, showers, and so on.



Fig 99—Chronic moniliasis of soles simulating common hyperkeratotic tinea pedis due to dermatophytes (Courtesy Dr Carmen C Thomas)

Vascular disease of the extremities, chronic hyperhidrosis and alcoholism reduce the probability of a rapid cure, but it should be emphasized that some cases of tinea pedis prove resistant to all therapeutic measures.

Treatment.—Prophylaxis is important. Careful drying of the toes after bathing, followed by the application of 10 per cent sodium propionate in talcum powder, is beneficial and will prevent most infections. Thymol-iodide, salicylic acid dusting powder may be used Ill-fitting shoes should not be worn, and exposure of the naked feet to floors, showers, etc., should be avoided. Socks should be changed daily, and attention should be given to early erosions and blisters.

DRY PAPULOSQUAMOUS LESIONS OF CHRONIC INTERTRIGINOUS LESIONS are treated best by using aqueous potassium permanganate soaks (1:4000) for one-half hour each night, followed by the application to the affected areas of Castellani's paint, one-half strength Whitfield's ointment or 10 per cent sodium propionate either in a water soluble base or in 10 per cent alcohol. A dusting powder, containing 15 per cent calcium propionate or 1 per cent thymol iodide and 3 per cent salicylic acid in talcum powder, should be applied the following morning. *Such a regime of treatment should be continued for at least* one week after the lesions have healed; the dusting powder may be used indefinitely as a prophylactic measure.

[illegible] stronger keratolytics, such [illegible] in aquaphor. Such ointments should be used after daily potassium permanganate soaks (1:4000) and mechanical débridement. Fissures may be treated by application of 5 per cent silver nitrate or tincture of iodine.

ACUTE ECZEMATOID and SECONDARILY INFECTED tinea pedis necessitates bed rest and elevation of the feet. The feet should be compressed continuously with warm potassium permanganate solution (1:4000), physiologic saline, 0.25 per cent Burow's solution or saturated boric acid solution. Mechanical débridement *rather than chemical* keratolytics should be used, and the tops of all vesicles, pustules and bullae should be clipped. Care must be exercised not to treat too vigorously, as severe, generalized dermatophytids may result from [illegible] therapy. After the acute lesions have subsided, treatment [illegible] the management of the [illegible] apy, in the hands of one especially trained in its use, in dosages of 75 roentgen units (one-fourth erythema dose), unfiltered, at weekly intervals of four to eight weeks may prove valuable. Desensitization to trichophytin often is useful in the treatment of resistant cases. Overtreatment should be *avoided and all medication stopped if signs of irritation develop*

TINEA UNGUIUM

(Onychomycosis, Trichophytosis Unguium, Onychosis Trichophyta, Ringworm of the Nails)

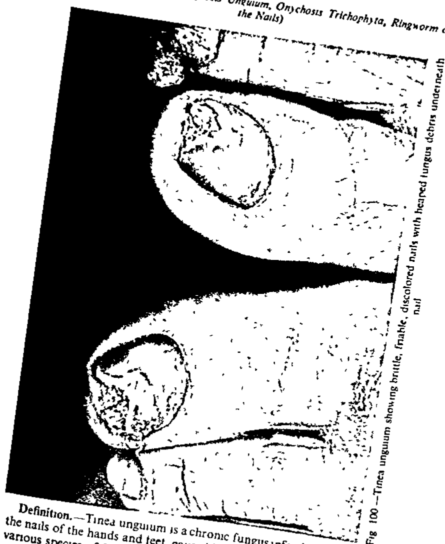


Fig 100 —Tinea unguium showing brittle, friable, discolored nails with heaped fungus debris underneath nail

Definition.—Tinea unguium is a chronic fungus infection, involving the nails of the hands and feet, caused by *Epidermophyton floccosum*, various species of *Trichophyton* and *Candida albicans*.

Geographic Distribution.—Tinea unguium occurs in all parts of the world.

Symptomatology.—The affected nails are discolored, lusterless, brittle, thickened, friable and may become pitted and grooved as a result of paronychial inflammation. Infection usually begins distally or at the lateral edge of the nail, and beneath the nail there is an accumulation of a cheesy epidermal detritus in which the causative fungus can be demonstrated. Such detritus usually does not occur in *C. albicans* infections of the nails (See MONILIASIS) In some instances, the top of the nail separates distally, leaving it thin, furrowed, ragged and deformed. (Fig. 100.) The patient usually gives a history of previous infection of the toes, feet or hands; toe nails are affected more often than finger nails, and one or more nails may be affected Paronychial involvement is uncommon except in infection due to *C. albicans*. Tinea unguium is the most resistant of all fungus infections and shows no tendency to spontaneous cure.

Differential Diagnosis.—The diagnosis of tinea unguium is suggested by the presence of deformed, thickened and discolored nails with or without associated paronychia, especially if the nail has a ragged, furrowed, dog-eared appearance and there is an accumulation of epidermal detritus beneath it.

Tinea unguium is simulated occasionally by psoriasis, onycholysis, acrodermatitis perstans, paronychia congenita, dystrophy following trauma or serious systemic disease, exfoliative dermatitis, chronic eczema and deformity and dystrophy following pyogenic infections of the paronychia, but demonstration of fungus elements in the débris beneath the nail proves the mycotic nature of the infection.

Prognosis.—The prognosis is poor despite evulsion of the affected nails or long periods of local treatment and x-ray therapy.

Treatment.—Careful local treatment should be followed assiduously by careful removal of infected nails and all the epidermal detritus beneath them. The nail should be filed daily to paper thin consistency. After filing, the nails should be soaked for one-half hour each day in potassium permanganate solution (1 4000). After soaking, an ointment containing 10 per cent sulfur and 10 per cent salicylic acid in equal parts of lanolin and white petrolatum should be rubbed into the affected nail for 3 minutes. Other medications which may be used are iodine (1 per cent) in alcohol or chrysarobin (20 per cent) in chloroform.

Fractional filtered X-RAY THERAPY, in the hands of experts, is a helpful adjunct Months of careful treatment often are necessary, and

If the condition persists, surgical evulsion is indicated. X-ray therapy and local treatment should be applied to the base of the new nail as it grows out, but recurrences are to be expected

TINEA CRURIS

(Eczema Marginatum, Jockey Itch, Dhobie Itch, Ringworm of the Groin, Gym Itch)

Definition.—Tinea cruris is a fungus infection, involving the groin, perineum and perianal region, caused by *Epidermophyton floccosum* and species of *Trichophyton*

Geographic Distribution.—Tinea cruris is found in all parts of the world, but the infection is more common in the tropics

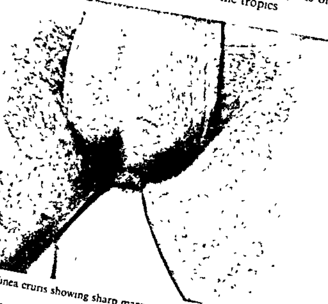


Fig 101 —Tinea cruris showing sharp margination and active periphery

Symptomatology.—The classic type of tinea cruris, caused by *E floccosum*, is characterized by well-marginated, elevated, papular, scaly patches of dermatitis with active, spreading peripheries studded with vesicles or vesicopustules The lesions usually are bilateral but not necessarily symmetrical (Fig 101), the central portions are brownish to red in color and covered with fine, branny, furfuraceous scales In acute infections, there is considerable erythema, but the



Fig. of a tinea cruris

older cases may show only lichenified, leathery and plaque-like lesions. The eruption may extend into the pubic areas and as far back as the sacrum, involving the scrotum or vulva but particularly the perianal intertriginous region In some instances, the lesions may appear as isolated vesicopustules without the typical marginated appearance Occasionally, the axillae may be involved and present a picture similar to that seen in the groin (Fig 102.) Sometimes the lesions may be white, soggy and macerated and resemble those caused by *Candida albicans*.

Perspiration, irritation from clothing, diabetes, neurodermatitis, leukorrhea and friction resulting from obesity frequently are predisposing factors. There may be moderate to intense itching.

Differential Diagnosis.—The clinical appearance of the lesion, with the sharp margination and active periphery, is diagnostic of tinea cruris, but erythrasma, moniliasis, lichen simplex chronicus, contact dermatitis, psoriasis and seborrheic eczema must be considered.

Prognosis.—With local treatment and sterilization of the clothing, the prognosis is good unless the affecting organism is *Trichophyton rubrum*

Treatment.—In the acute erythematous phase, potassium permanganate (1:4000) sitz baths twice daily should be followed by the application of 1 per cent aqueous gentian violet solution and soothing lotions Continuous wet compresses may be necessary at the outset In the chronic low grade processes, potassium permanganate *(1.4000) sitz baths twice daily followed by application of Castellani's* paint and 15 per cent calcium propionate in talcum powder or one-half strength Whitfield's ointment and 15 per cent calcium propionate dusting powder usually will effect a cure in from one to two weeks Pragmatar ointment and thymol iodide, salicylic-acid dusting powder may be used in the same manner. Local hygiene is important Occasionally, a particularly resistant infection can be controlled by fractional X-RAY THERAPY. The testes should be protected by careful screening, and roentgen therapy should be carried out by one especially trained in its use. The patient should not use soap excessively. Occasionally, desensitization procedures are of value

TINEA CORPORIS

(*Tinea Circinata, Tinea Glabrosa, Ringworm of the Body, Trichophytosis Corporis, Scherende Flechte* [Ger], *Herpes Circine Trichophvtique* [Fr])

Definition.—Tinea corporis, caused by various species of *Trichophyton* and *Microsporum*, is a fungus infection which involves the



Fig 103 —Annular vesiculopustular tinea corporis.

glabrous skin and produces lesions which vary from those of simple scaling to deep granulomata.

Geographic Distribution.—Tinea corporis is more common in tropical and temperate climates

Symptomatology.—The commonest manifestation of tinea corporis is the annular erythematous, papulosquamous lesion. (Fig. 103) The central area is scaly, and the advancing active periphery usually is studded with crusting vesicles and pustules The lesions vary from 0 5 to 5 cm in size and may be single or multiple Such lesions may begin on any part of the body and coalesce to form arciform configurations (Fig. 104) Children are affected more often than adults, and the disease frequently is acquired from animals

Small, circinate, annular lesions may enlarge into erythematous, squamous lesions which may become solid and plaque-like, or they may become eczematoid and spread peripherally in circinate fashion but without central clearing Some of the lesions show only dry superficial scaling; others appear moist and crusted In rare instances, the lesions may become granulomatous and produce ulceration of the skin Most lesions are relatively asymptomatic although some of them cause itching

Differential Diagnosis.—The diagnosis of tinea corporis is suggested by the appearance on the glabrous skin of annular papulosquamous lesions with vesiculopustular and crusted peripheries and a scaly, clearing center.

Psoriasis, pityriasis rosea, granuloma annulare, neurodermatitis localized, annular secondary syphilis, annular lichen planus, seborrheic dermatitis, contact eczema, drug eruptions, or erythema annulare centrifugum may resemble tinea corporis, but can be excluded by demonstrating the fungus by direct examination or by culture

Prognosis.—With careful treatment, the prognosis is good

Treatment.—The best results are obtained by removing the crusts and scales by soap and water twice daily and, following the debridement, by local application of the medication prescribed An ammoniated mercury ointment (5 per cent), pragmatar ointment, 3 per cent sulfur and 3 per cent salicylic acid in aquaphor or 3 5 per cent tincture of iodine usually results in complete cure in two weeks It is important that the ointment be rubbed in vigorously and not simply smeared over the area Sodium propionate (10 per cent) in alcohol or in ointment form may be used If results are not obtained by using one of the medications described above, one of the other preparations should be tried



Fig 104—Tinea corporis showing coalescence of annular vesiculopustular lesions

TINEA IMBRICATA

(Tokelau, Burmese, Chinese, India Ringworm, Scaly Ringworm, Lafa Tokelau, Tinea Circinata Tropical, Gogo)

Definition.—Tinea imbricata is a superficial fungus disease, caused by a single species of *Trichophyton, T concentricum*, which is characterized by the presence of concentrically arranged rings of papulosquamous patches which are scattered over the body.

Geographic Distribution.—Tinea imbricata is a disease of the tropics, particularly in the South Pacific Islands, Southern China, Ceylon, South Africa and South and Central America

Symptomatology.—Tinea imbricata presents a characteristic picture resulting from the rapid development of polymorphic and polycyclic patches from coalescence of adjacent concentric rings. (Fig 105.) There is little erythema but itching may be intense The nails are involved only rarely, and the hair usually is spared The disease most often starts with the appearance of brownish maculopapules, followed by a detachment of the central portion and a fissure spreading toward the periphery. The margins are elevated and resistance can be felt by passing the fingers over the lesions from the central portion to the periphery. Lamellae of epidermis become detached, the free border being directed toward the center A brownish ring surrounds the active, spreading periphery If the eruption is very diffuse, the skin may take on the appearance of ichthyosis

Differential Diagnosis.—The clinical appearance of the peculiar polymorphic, polycyclic, concentric rings with no evidences of inflammatory changes is so characteristic of tinea imbricata that it can hardly be confused with any other disease

Prognosis.—Tinea imbricata is extremely resistant to treatment, and relapse is common.

Treatment.—Strong keratolytics and fungicides, such as 10 per cent chrysarobin in aquaphor, 5 per cent sulfur and 5 per cent salicylic acid in aquaphor, Castellani's paint or full strength Whitfield's ointment, should be applied twice daily.

TINEA BARBAE

(Tinea Sycosis, Tinea Barbae Trichophytica, Barbers' Itch, Trichophytie Sycosique [Fr], Parasitare Bartfinne [Ger], Ringworm of the Beard, Sycosis Parasitica)

Definition.—Tinea barbae is a chronic fungus infection of the bearded area of the face and neck, caused by various species of *Trichophyton* and *Microsporum* and characterized by both superficial



Fig 105 —Tinea imbricata on arm showing concentric scaling lesion (After Figueroa and Conant, The American Journal of Tropical Medicine, 20)

lesions, resembling those of tinea corporis, and deeper types of infection resulting from involvement of the hair follicles.

Geographic Distribution.—Tinea barbae is uncommon in America, but frequently is seen in the Balkans, Central Europe and the countries around the Mediterranean basin.

Symptomatology.—The SUPERFICIAL TYPE of tinea barbae produces lesions which closely resemble those of tinea corporis on the glabrous skin. There is a scaling central area surrounded by an active, vesiculopustular border. The hair in such infected areas may be brittle and lusterless, and areas of alopecia may develop in the central portions.

The DEEP TYPE of infection, rarely seen in this country, is characterized by the presence of deep, follicular pustules which result in abscess formation and the production of nodular, kerion-like lesions (Fig. 106.) Such lesions feel boggy and the hairs, which are brittle and easily epilated, have a whitish, bulbous root, draining sinuses develop in such undermined tissue, and extrusion of purulent material from the follicle can be accomplished by slight pressure. The lesions usually are limited to one area of the face, particularly the maxillar and submaxillary regions, but they may involve almost the entire bearded area. The early lesions cause some itching and the deeper infections are exquisitely tender. The upper lip is involved only rarely, differing in this respect from sycosis vulgaris.

Differential Diagnosis.—The presence in the bearded regions of scaly lesions surrounded by active peripheral borders or deep, follicular pustules with brittle, lusterless, easily epilated hair suggests the diagnosis of tinea barbae. If the causative organism is *Microsporum canis* or *Trichophyton violaceum*, fluorescence with ultraviolet light is present; if *T. mentagrophytes*, *T. rubrum* or other fungi are causing the lesion, fluorescence does not occur.

The diagnosis of sycosis vulgaris due to pyogenic organisms can be eliminated by finding the fungus elements by direct microscopic examination and by culture. Contact dermatitis, alopecia areata, seborrheic dermatitis, anthrax, actinomycosis, ioderma, bromoderma, severe cystic acne and pustular syphilis also can be excluded by mycologic examination.

Prognosis.—The prognosis depends on many factors, such as the degree of cooperation on the part of the patient, the extent of the disease, when treatment is started and the species of fungus causing the infection. In general, species of *Trichophyton* producing the endothrix type of hair infection are harder to eradicate than those producing infections of the ectothrix type.



Fig. 106.—Tinea barbae of chin showing boggy granulomatous character.

TINEA CAPITIS

(Trichophytosis Capitis, Tinea Tonsurans, Ringworm of the Scalp)

Definition.—Tinea capitis is a fungus infection of the scalp and hair, caused by species of *Trichophyton* and *Microsporum*, which is characterized by scaly, erythematous lesions, alopecia and sometimes deep, ulcerative, kerion-like eruptions.

Geographic Distribution.—The infection has a world-wide distribution, but occurs more commonly in Central Europe, the Balkans, Poland, Russia and in the countries around the Mediterranean basin.

Symptomatology.—Tinea capitis usually occurs in childhood and rarely is found after puberty, except in infections caused by *Trichophyton Schoenleini.* The earliest lesion usually is seen as a small, scaling, erythematous papule, perforated by a hair. Such papules spread peripherally to form patches (Fig. 107); the hair becomes lusterless, brittle, breaks off easily and becomes loosened so that it can be epilated readily. Itching may be intense, and alopecia usually develops in the infected areas. Infections caused by *Microsporum canis* and *M. gypseum* produce marked inflammatory changes, in contrast to those caused by *M. Audouini* which usually are low grade scaling lesions. Fluorescence usually is demonstrated by the Wood's light. The deep, ulcerative, inflammatory reactions produce boggy, non-specific, kerion-like lesions. Since tinea capitis is very contagious (Fig. 108), any scaling alopecia occurring in a child should be considered to be tinea capitis until proved otherwise. The disease occurs most often in the poor, especially those living under overcrowded conditions. The organisms can be demonstrated in the hairs by microscopic examination in 10 to 40 per cent potassium hydroxide.

Differential Diagnosis.—The diagnosis of tinea capitis is suggested by the finding, particularly in children, of scaling, erythematous patches of alopecia in the scalp with brittle, lusterless hair or deep, boggy, kerion-like, ulcerative lesions.

Seborrheic dermatitis, psoriasis, lupus erythematosus, alopecia [illegible]

Prognosis.—Tinea capitis caused by the fungus from animal sources (*M. canis, M. gypseum*) is cured easily and may involute spontaneously. Fungi of the human type, *M. Audouini*, or species of *Trichophyton* of either the endothrix or the ectothrix type seldom show a tendency to self-cure and require prolonged treatment.



Fig 108 —Tinea capitis due to *Microsporum Audouini* in three members of the same family, demonstrating the infectiousness of the disease (Courtesy of Dr. Carmen C. Thomas)

Treatment.—*M. canis* and *M. gypseum* infections should be treated by daily scrubbing with soap and water to remove crusts and scales. Manual epilation of the affected hairs should be followed by compresses of saline or potassium permanganate (1:4000) for one-half hour and this treatment followed by vigorous rubbing in of 10 per cent ammoniated mercury ointment, 5 per cent iodine in aquaphor or 3 per cent salicylic acid and 3 per cent sulfur ointment or pragmatar ointment.

If the etiologic agent is not *M. canis* or *M. gypseum*, epilation, using the MacKee technic of x-ray therapy, should be done by an expert roentgenotherapist. Roentgenotherapy should be followed by manual epilation of remaining hairs, daily shampooing and the application of a mild ointment, such as 5 per cent ammoniated mercury. Residual infection should be checked by using the Wood's ultraviolet light filter. At least two negative microscopic examinations should be obtained before the patient is released as cured. Children should not be allowed to attend school, and all hair, combs and brushes should be sterilized or burned.

TINEA FAVOSA

(Favus Honeycomb Ringworm, Teigne Faveuse [Fr.], *Erbgrind* [Ger.])

Definition.—Tinea favosa is a chronic fungus infection, caused by *Trichophyton Schoenleini*, *T. violaceum* or *Microsporum gypseum*, usually limited to the scalp where it produces characteristic yellowish, cup-shaped crusts (scutula) which have a peculiar "mousy" odor and frequently show considerable atrophy; occasionally, the glabrous skin and nails may be involved

[illegible] commonly occurs in

in the United States and England, it occurs almost exclusively in Russian and Polish immigrants. Malnutrition, filth and neglect play important roles in the occurrence and propagation of the disease.

Symptomatology.—Tinea favosa is most common in the scalp where it begins as minute, subcuticular, pinpoint, yellowish-red puncta which develop into yellowish, cup-shaped, elevated crusts of varying size. One or more hairs usually protrude from the friable, concave crusts (scutula) (Fig 109), and removal of the crusts reveals depressed, red, moist bases. The hair soon becomes involved, appears lusterless and ultimately sheds. If untreated, the disease spreads all over the scalp with resultant scarring and baldness. In contradistinc-

[illegible]

(Fig. 110) and it is important that it be recognized as a type of tinea favosa.



Fig 109 —Favus of scalp showing atrophy, alopecia and scutula (After Andrews, Diseases of the Skin, 2d ed , Philadelphia, W B Saunders Co)

Tinea favosa of the glabrous skin produces vesicular, papular and [illegible]

indistinguishable from other forms of tinea ungium

Differential Diagnosis.—The diagnosis is easy when the lesions show the typical yellowish scutula, have a "mousy" odor and show

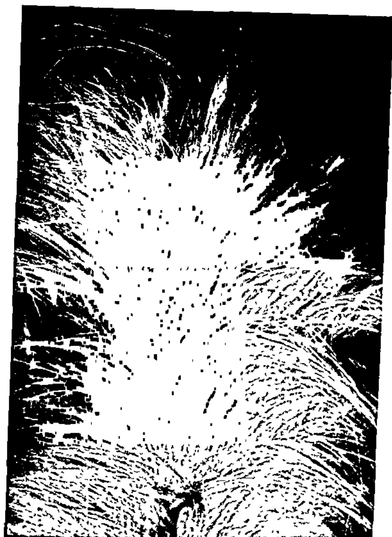


Fig 110 —Scaling seborrheic type of tinea favosa.



Fig 111 —Tinea favosa of glabrous skin showing typical scutula (Photo by Dr Cram from MacKenna, Diseases of the Skin, Baillière, Tindall & Cox)

fluorescence with the Wood's light. Tinea capitis due to other fungi should be considered, but can be excluded by the formation of scutula and the "mousy" odor in tinea favosa. If atrophy is marked, pseudopelade, lupus erythematosis or lupus vulgaris must be considered. Seborrheic eczema and pyodermias of the scalp also may simulate tinea favosa.

Prognosis.—In well-treated cases, the ultimate prognosis of favus *of the scalp is favorable, but considerable scarring may have resulted* before treatment was begun. The prognosis in favus of the glabrous skin is the same, but infections of the nails are very difficult to cure.

Treatment.—Since the hair is involved in almost every instance of *favus of the scalp,* EPILATION *of the hair is essential. Such epilation* is best performed by x-ray therapy, in the hands of one especially trained in its use, employing the MacKee technic. Remaining hairs must be epilated manually, and ointments, such as those described for tinea capitis, should be rubbed in well and not merely applied locally.

For the treatment of the GLABROUS SKIN, the use of warm, wet compresses, mechanical removal of the scutula and the application of suitable ointments are satisfactory.

Involvement of the NAILS requires evulsion of the affected nail, followed by fractional x-ray therapy and local application of ointments.

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Chapter XVII

IMMUNOLOGY OF THE DERMATOMYCOSES

Serology.—Attempts to demonstrate agglutinins, precipitins or complement fixing antibodies in the sera of patients with superficial dermatomycoses have resulted uniformly in failure. Such failures may be technical in origin since the preparation of standardized antigens from moldlike cultures is difficult and such antigens may lack the sensitivity required to give positive results in the test tube. On the other hand, the lack of antibody production may be due to the fact that the infection is superficial and the body cells are not stimulated to produce excess antibodies in sufficient amounts to be detected in the circulating blood.

Ayres and Anderson, in 1934, reported that circulating fungistatic antibodies could be demonstrated in patients with epidermophytosis if phytids also were present. Such antibodies were demonstrated by noting inhibition of growth of the fungus on Sabouraud's slants containing 8 per cent of the patient's serum Lewis and Hopper, however, obtained irregular results by using this method, and observed that samples of serum from some normal individuals also caused fungistasis.

Hypersensitivity.—The development of cutaneous hypersensitivity to the fungus or fungus products is a complicating factor in many patients with superficial dermatomycoses, and such hypersensitive patients show skin reactions when tested with fungus vaccine, "Trichophytin" or "Oidiomycin." Immediate "wheal-like" reaction may be obtained in a few patients, but in most instances the delayed type *of reaction appears in about twenty-four to forty-eight hours,* at which time the skin at the site of injection appears erythematous, and may persist for several weeks as a patch of eczematoid dermatitis. The immediate wheal-like reaction can be transferred passively by using the Prausnitz-Kustner technic; the delayed type of reaction is not passively transferable.

De Lamater and Benham have studied the problem of cutaneous *sensitization in experimental* animals and have reviewed critically the literature on the subject. Infection was produced in guinea pigs, *and* the animals were re-inoculated at varying times after healing of the primary lesion The lesions produced by re-inoculation resembled the

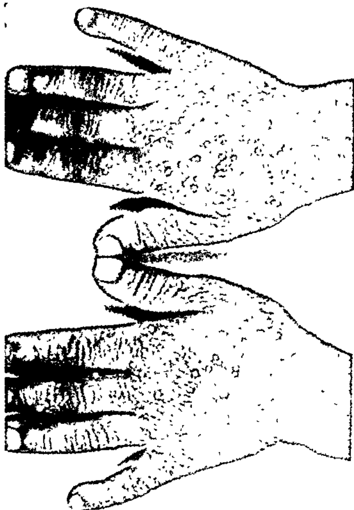


Fig 112 — Early dermatophytid of hands showing grouped vesicular lesions.

primary lesions except that they developed more rapidly, healed more quickly and fungi could be demonstrated only *rarely in the secondary* lesions.

Dermatophytids.—Dermatophytids are secondary eruptions occurring in specifically sensitized individuals as a result of the hematogenous spread of fungi or their allergenic products *from a primary* focus. In a patient with dermatophytids, a primary fungus lesion

Oidiomycin Such "ids" may follow irritation of the primary focus brought on by trauma or overtreatment, and disappear after clearing of the fungi from the primary lesions. That "ids" may result from actual transfer of fungus elements through the blood stream has been demonstrated occasionally by blood culture.

The fingers and hands are the commonest sites of the "id" eruption

a series of vesicles (pomphlox type) appearing along the sides of the fingers or grouped vesicular lesions on any or all parts of the body but particularly on the fingers and hands. (Fig 114.) Such vesicles are tense, edematous and filled with clear or cloudy fluid The vesicles may be deep; they usually itch intensely and sometimes are painful Secondary infection, lymphangitis and lymphadenitis may develop as the acute phase subsides and scaling patches, resembling eczematoid dyshidrosis, may form. Occasionally, frank eczematoid and erysipeloid lesions are seen

TREATMENT is directed primarily to the initial focus and must be conservative to avoid exacerbation of the "id" eruption. Such secondary eruptions should be treated by warm, wet compresses, such as saline or boric acid solution, soothing lotions and creams The affected parts should be protected, soap and water avoided and débridement and rest supplemented by efforts to avoid secondary infection.

Calcium gluconate, injections of whole blood and roentgen therapy may hasten the involution and aid in desensitization Desensitization by vaccine, if attempted, must be done with extreme caution.

Trichophytin and Oidiomycin Tests.—Sensitivity is tested for by the intracutaneous injection of a standard "Trichophytin" or "Oidio-

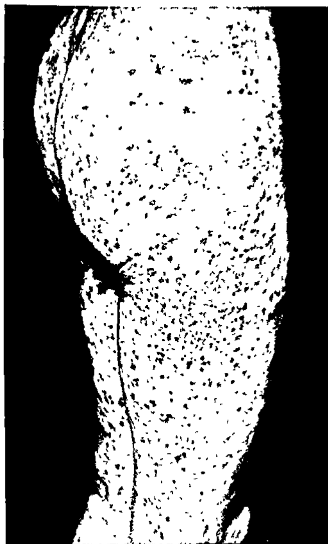


Fig. 113 —Generalized dermatophytid demonstrating grouped follicular papulo-vesicular response



Fig. 114.—Severe explosive bullous dermatophytid of hands.

mycin" vaccine. Commercial preparations, such as those prepared by Lederle and Metz are satisfactory and are better standardized than autogenous vaccines prepared in local laboratories A dilution of 1:1000 usually gives a specific reaction although a 1:100 dilution may be necessary to obtain a positive reaction One-tenth cc of the diluted "Trichophytin" or "Oidiomycin" is injected intracutaneously and observed after 15 minutes for an immediate wheal reaction, at 24 and 48 hour intervals and later for the delayed erythematous or eczematous responses. Delayed reactions sometimes develop as much as a week later Sterile broth may be used as a control.

Desensitization.—In persons found to be sensitive to preparations of "Trichophytin" and "Oidiomycin," it often is desirable to attempt desensitization as an adjunct in treatment. Although there is considerable controversy as to the value of such desensitization therapy, it is a justifiable measure in recalcitrant infections which are not responding to regular treatment

The dilution of the vaccine to be administered depends on the reaction of the individual when skin tested, but the dose may be modified, depending upon the reactions obtained during the course of treatment In patients giving a 4-plus reaction, concentrations no higher than 1 10,000 should be used for the initial injections to avoid violent reactivations of the "id" reactions. In general, the dilutions of vaccine and schedules of therapy recommended for desensitization in the dermatomycoses are the same as those outlined in the desensitization of patients to the systemic mycoses (See desensitization schedule under North American blastomycosis)

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Chapter XVIII

MYCOLOGY OF THE DERMATOMYCOSES

The dermatomycoses are caused by a closely related group of fungi, the *Dermatophytes*, which produce only superficial infections of the skin or its appendages and do not invade the deeper tissues or the internal organs.

At first, certain organisms were described and classified into a number of genera, including *Microsporum, Trichophyton, Achorion, Epidermophyton* and *Endodermophyton*. Under each of these genera species were placed according to the gross appearance of the fungi in culture and the clinical characteristics of the lesions from which they were isolated. This method of classification resulted in confusion since it permitted identical fungi to be placed in different genera according to the types of lesions from which they were isolated, and different fungi isolated from similar lesions were placed in the same genus irrespective of their cultural characteristics. A classification was then proposed which would take into account only the cultural characteristics of the fungi as they developed on artificial media. Such classifications, however, resulted in increasing the confusion because several new genera were offered in the place of the old familiar names and not enough attention was paid to the morphologic variations which occur in cultures of the dermatophytes.

A simplified classification has been made possible recently by culturing the fungus and selecting certain specific morphologic features as criteria for generic differentiation. By this method Emmons clearly showed that only 3 genera need be considered, *Microsporum, Trichophyton* and *Epidermophyton*, each of which can be distinguished morphologically by its conidia and other accessory structures The number of species has been reduced by Langeron and Milochevitch, Ota and Kawatsuré and others who have recognized as variations of valid species several fungi described elsewhere as new species. (Table IV.)

[illegible] examination of infected [illegible] aused [illegible] scalp should be epilated by forceps Skin lesions should be cleansed with 70 per cent alcohol and material obtained by scraping the edges of the inflamed areas with a scalpel, the edge of a slide or any available

scraper. The tops of vesicular lesions should be removed by means of small, curved manicure scissors. In scraping lesions of the toe webs, macerated areas should be avoided and the material taken from the edges of the lesions along the healthy skin of the toes or bottom of the foot. In obtaining material from infected nails, friable or discolored areas should be selected and scraped with the edge of a microscopic slide or scalpel; débris beneath undermined areas or under thick, hyperkeratotic nails also should be studied.

TABLE IV. DERMATOPHYTES

Trichophyton Malmsten, 1845
(Hair—Skin—Nails)

- A. Gypseum Group
  - 1. *T. mentagrophytes*
- B. Rubrum Group
  - 2. *T. rubrum*
- C. Crateriform Group
  - 3. *T. tonsurans*
  - 4. *T. epilans*
  - 5. *T. Sabouraudi*
  - 6. *T. sulfureum*
- D. Faviform Group
  - 7. *T. Schoenleini*
  - 8. *T. concentricum*
  - 9. *T. ferrugineum*
  - 10. *T. violaceum*
- E. Rosaceum Group
  - 11. *T. Megnini*

Microsporum Gruby, 1843
(Hair—Skin)

1. *M. Audouini*
2. *M. canis*
3. *M. gypseum*

Epidermophyton Sabouraud, 1910
(Skin—Nails)

1. *E. floccosum*

All materials for direct examination should be placed [illegible]

heated. A clue to the genus *Trichophyton* or *Microsporum* may be obtained from the appearance of the fungus in the INFECTED HAIR, but species identification can be made only after the fungus has been isolated in pure culture. Species of *Microsporum*, *Trichophyton* or *Epidermophyton* present identical appearances in infected skin or nails, and generic or specific identification can be made only by culture. The appearance of the dermatophytes in infected materials is described below.

A. *Trichophyton* Species of *Trichophyton* attack the hair, skin and nails. Infected hairs may show arthrospores arranged in parallel rows inside the hair (endothrix type) or arranged in parallel rows outside the hair (ectothrix type) and appearing either as chains of small arthrospores (microides type) or chains of large arthrospores (megi

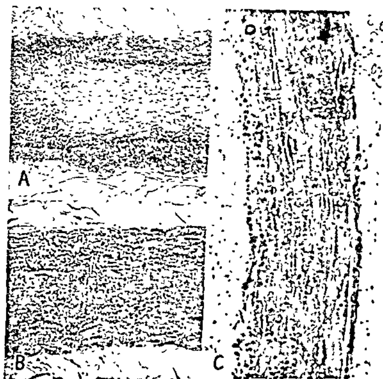


Fig 115 —Infected hair *A Microsporum* Small spores forming sheath around hair × 110 *B Trichophyton* Parallel chains of arthrospores inside hair (endothrix) × 170 *C Trichophyton* Favus hair showing mycelial elements and numerous bubbles which are characteristic × 220

spore type) (Fig. 115*B*, *C*) In the skin and nails, species of *Trichophyton* appear as segmented, branching mycelial elements which may or may not break up into arthrospores (Fig 116*A*) Such forms are indistinguishable from those of *Microsporum* and *Epidermophyton*

B. *Microsporum* Species of *Microsporum* attack only the hair and skin Infected hairs show the fungus as a mosaic sheath of small

spores surrounding the hair shaft. (Fig. 115*A*.) In the skin, the fungus appears only as segmented, branching mycelial elements and cannot be distinguished from those of *Trichophyton* and *Epidermophyton*. (Fig. 116*A*.)



Fig 116.—Infected skin *A*. Branching hyphae that might yield in culture species of *Microsporum*, *Trichophyton* or *Epidermophyton floccosum* × 200 *B* Typical close septate hyphae of *Trichophyton concentricum* in skin × 450 C Mosaic fungus An artifact often seen in potassium hydroxide preparations of skin × 200

C. *Epidermophyton* The hair is not infected by *Epidermophyton* which attacks only the skin and nails The fungus appears in such materials as segmented, branching mycelial elements, identical in appearance with the forms seen in *Microsporum* infections of the skin and *Trichophyton* infections of the skin or nails (Fig 116*A*.)

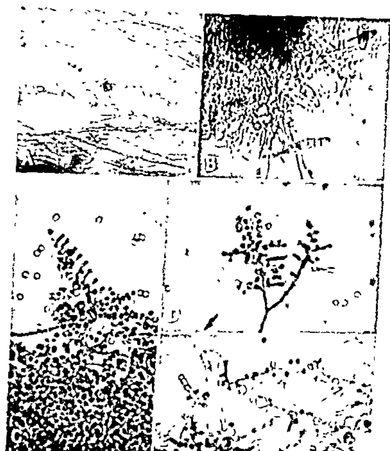


Fig. 117.—Microscopic morphology of the genus *Trichophyton* *A* Racquet hyphae and nodular body. *B.* Multiseptate, clavate macroconidia *C.* Spiraled hyphae × 375. *D.* Conidiophores which produce clusters of microconidia (en grappe) × 375. *E* Hyphae with lateral microconidia (thyrses) × 375.

Cultures.—Material may be cultured directly from the lesions or placed between wrapped, sterile slides for five to seven days to permit desiccation of bacterial contaminants. For successful isolation, it is recommended that three to four small fragments be planted short distances apart on each of three Sabouraud's glucose agar slants. The cultures should be maintained at room temperature and kept for at least 2 weeks. The cultures should be examined daily for evidence of growth from the edges of the planted materials and, after growth is established, transplants should be made to fresh media for pure culture study.

Cultures are examined microscopically by removing a portion of the aerial growth with a straight sterile transfer wire. The material is placed on a slide in a drop of lactophenol cotton blue and the matted mycelial mass teased or separated with dissecting needles. A cover glass should be added and the preparation heated over a low flame to drive out air bubbles and produce greater penetration of the stain. Primary cultures of the dermatophytes should be examined microscopically as soon as reasonable growth is obtained. Such cultures soon become pleomorphic, overgrown with a sterile, white mycelium and the characteristic spore forms, used for identification, are lost. Differentiation of the genera and species of dermatophytes is based upon gross colony characteristics and the microscopic morphology. The diagnostic cultural features are described below.

TRICHOPHYTON
(Malmsten, 1845)

Grossly, the fungus may appear cottony, granular or powdery, or glabrous, smooth and waxy. Pigmentation varies greatly and cultures may be white, pink, red, purple, violet, orange, yellow or brown. Such pigmentation may become lost on transfer, vary in intensity, appear only on the reverse of the colony, involve the aerial mycelium, or the pigment may diffuse throughout the media. The gross character of the colonies serves to divide the genus into five groups: gypseum, rubrum, crateriform, faviform and rosaceum.

On microscopic examination, microconidia (aleuriospores) are numerous and are seen as small, single-celled, thin-walled, hyaline, subspherical to clavate conidia, 2 by 4 μ, which are borne in grape-like clusters (en grappe) or singly from the sides of the hyphae (thyrses) (Fig 117*D*, *E*).

Macroconidia (fuseaux) are rare, or lacking in some species, and appear as large, multicelled, smooth, thin-walled, hyaline, clavate

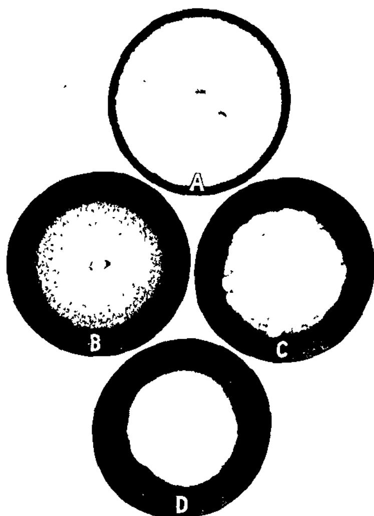


Fig 118.—*A Trichophyton mentagrophytes* (gypseum type) on Sabouraud's glucose agar *B T mentagrophytes* (asteroides-type) on Sabouraud's glucose agar *C. T mentagrophytes* (interdigitale-type) on Sabouraud's glucose agar *D T rubrum* on Sabouraud's glucose agar.

conidia, 4 to 6 μ in width by 10 to 50 μ in length (Fig. 117*B*) Other structures, such as racquet mycelium, chlamydospores, nodular bodies and coiled hyphae, also may be seen.

I. Gypseum Group.—The cultures are powdery to granular, light buff to rose-tan in color, and may vary from a fluffy, cottony type to velvety and pure white. The reverse of the colony is wine-colored to brownish. (Fig. 118*A*, *B*, *C*.)

Powdery and granular cultures develop numerous microconidia in clusters and singly on the hyphae There usually are coils, nodular bodies and chlamydospores but few macroconidia. Cottony colonies develop such structures to a lesser degree and may show none of them. A single species with numerous synonyms is placed in this group.

Trichophyton mentagrophytes (Robin) Blanchard, 1896. Synonymy.—*Microsporon mentagrophytes* Robin, 1853; *Achorion Quinckeanum* Blanchard, 1896; *Trichophyton felineum* Blanchard, 1896, *Trichophyton gypseum* Bodin, 1902; *Trichophyton equinum* Gedoelst, 1902, *Trichophyton granulosum* Sabouraud, 1909, *Trichophyton radiolatum* Sabouraud, 1910, *Trichophyton lacticolor* Sabouraud, 1910; *Trichophyton niveum* Sabouraud, 1910, *Trichophyton radians* Sabouraud, 1910, *Trichophyton denticulatum* Sabouraud, 1910, *Trichophyton persicolor* Sabouraud, 1910; *Trichophyton farinulentum* Sabouraud, 1910, *Trichophyton asteroides* Sabouraud, 1910, *Trichophyton interdigitale* Priestley, 1917, *Trichophyton* "C" Hodges, 1921; *Trichophyton Kaufmann-Wolf* Ota, 1922; *Trichophyton pedis* Ota, 1922

II. Rubrum Group.—Cultures are cottony to velvety but sometimes develop a powdery appearance. Reddish to purple pigmentation develops on the reverse of the colony and may spread into the marginal hyphae. Occasionally, the aerial mycelium becomes pinkish in color in old cultures. (Fig. 118*D*.) Primary cultures develop numerous microconidia in clusters and singly along the hyphae, few

—*Epidermophyton rubrum* Castellani, 1910, *Trichophyton purpureum* Bang, 1910, *Epidermophyton Perneti* Castellani, 1910, *Trichophyton rubidum* Priestley, 1917; *Epidermophyton salmoneum* Froilano de Mello, 1921; *Trichophyton* "A" Hodges, 1921; *Trichophyton* "B" Hodges, 1921, *Trichophyton marginatum* Nuijs, 1921; *Trichophyton plurizoniforme* MacCarthy, 1925, *Trichophyton lanoroseum* MacCarthy, 1925, *Trichophyton coccineum* Katoh, 1925; *Trichophyton*

spadix Katoh, 1925; *Trichophyton multicolor* Magalhaes and Neues, 1927; *Trichophyton Kagawaense* Fujii, 1931.

III. Crateriform Group.—Cultures show various degrees of heaped or sunken central growth with folding of the surface. The colonies are velvety to powdery and may vary in color from white, cream, yellow, primrose or red to brown.

... *ies show numerous microconidia* ... on short sterigmata, and micro- ... croconidia are rare or lacking. Chlamydospores are found *throughout the culture, and terminal* swelling of the hyphae into club-shaped ends is frequent. The crateriform group has four species, each with numerous synonyms.

1. *Trichophyton tonsurans* Malmsten, 1845.

The colony at first appears velvety and white but becomes powdery, develops a cream to yellow color and, characteristically, shows a central depression with elevated rim forming a crater. Different strains vary slightly by being more folded, dry or cracked on the surface, ...

... —*Tricho-* ... n Sabou- ... *hophyton umbilicatum* Sabouraud, 1910; *Trichophyton regulare* Sabouraud, 1910, *Trichophyton exsiccatum* Sabouraud, 1910, *Trichophyton polygonum* Sabouraud, 1910

2. *Trichophyton epilans* Boucher & Mégnin, 1887

The colony at first appears somewhat crateriform, but becomes crumpled with irregular folds, assuming a cerebriform surface. The color is at first white but turns cream to yellowish, the first velvety ... cracked and granular with irreg- ...

The colony at first is small, hemispheric and velvety with few central projections of tufts of hyphae (coremia). Later it becomes powdery, heaped (acuminate) and the white color changes to cream or ...

... chard, 1896. Synonym).—*Trichophyton pilosum* Sabouraud, 1910.

4. *Trichophyton sulfureum* Sabouraud, 1910.

At first, the colony is velvety with a central red nodule, the rest of the culture showing a delicate primrose color. Later it becomes powdery, folded with small central crater, and becomes sulfur yellow in color. The central reddish pigment is lost on transfer, but the sulfur yellow, powdery aspect persists.

IV. **Faviform Group.**—Cultures of this group are slow growing, glabrous, waxy, heaped and folded. Later, the surface may become covered with velvety mycelium. The pigmentation varies greatly and may be white, yellow, brown, orange or violet.

Microscopically, only hyphal swelling and numerous chlamydospores and so-called "favic chandeliers" can be seen in some species. Microconidia of the *Trichophyton* type have been reported occasionally in most species. This group has four species, each with numerous synonyms.

1. *Trichophyton Schoenleini* (Lebert) Langeron and Milochevitch, 1930.

The colonies at first are heaped, glabrous and cerebriform and are yellowish-white to brownish in color. (Fig. 119*A*.) On transfer, the surface becomes velvety, heaped and wrinkled with many radiating grooves. (Fig. 119*B*.)

[illegible]" are supposed to be of [illegible]

[illegible], Langeron and Milochevitch, 1930. Synonymy.—*Oidium Schoenleini* Lebert, 1845; *Achorion Schoenleini* Remak, 1845, *Trichophyton album* Sabouraud, 1908; *Trichophyton ochraceum* Sabouraud, 1908; *Trichophyton discoides* Sabouraud, 1910.

2. *Trichophyton concentricum* Blanchard, 1896.

The colony is heaped, deeply folded, glabrous and white at first, but becomes deep brown in the center with cream-colored, somewhat powdery periphery; it may be grossly and microscopically identical with many strains of *T. Schoenleini* (Fig. 119*C*, *D*.) The pigment in the agar becomes deep amber in color.

Trichophyton concentricum Blanchard, 1896. Synonymy.—*Trichophyton Mansoni* Castellani, 1905, *Trichophyton Castellani* [illegible]

Mansoni Castellani, 1919; *Endodermophyton tropicale* Castellani, 1919, *Endodermophyton Roquettei* Fonseca, 1925

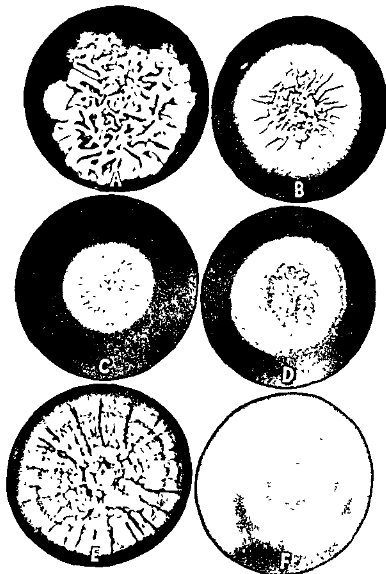


Fig 119.—*A Trichophyton Schoenleini*, primary isolation on Sabouraud's glucose agar *B T Schoenleini* after several transfers on Sabouraud's glucose agar *C. T concentricum* on Sabouraud's glucose agar, twenty-seven days *D. T concentricum* on Sabouraud's glucose agar, forty days *E T ferrugineum* on Sabouraud's glucose agar *F T violaceum* on Sabouraud's glucose agar

3. *Trichophyton ferrugineum* (Ota) Langeron and Milochevitch, 1930

The pigmentation at this time may appear in zones.

Trichophyton ferrugineum (Ota) Langeron and Milochevitch, 1930. Synonymy.—*Microsporum ferrugineum* Ota, 1921; *Microsporum japonicum* Dohi and Kambayashi, 1921; *Microsporum aureum* Takeya, 1925; *Microsporum orientale* Carol, 1928.

4. *Trichophyton violaceum* Sabouraud, 1902.

The colony at first is heaped, folded, glabrous and waxy, and violet in color. Later, it may become velvety as aerial mycelium develops (Fig. 119*F*)

Trichophyton violaceum Sabouraud, 1902. Synonymy.—*Trichophyton glabrum* Sabouraud, 1902, *Achorion violaceum* Bloch, 1911; *Trichophyton Gourvili* Catanei, 1933

V. Rosaceum Group.—Colonies at first are cottony to velvety and pure white in color. Later they become pale rose to delicate pink, and the reverse of the agar is a "currant violet" or "raspberry rose." Some strains become somewhat cerebriform and the surface cracks

Microscopically, many microconidia occur in clusters and singly; there are few macroconidia; racquet hyphae and chlamydospores are seen

This group is difficult to place. *Achorion gallinae* Sabouraud, 1910 (*Epidermophyton gallinae* Mégnin, 1881) is said to differ from *Tri-*

identified as *T. rosaceum* (Fig. 143*A*, *B*) This error should be avoided

If *Epidermophyton gallinae* Megnin, 1881, is the same as *Trichophyton rosaceum* Sabouraud, 1910, then the correct species name would be *Trichophyton gallinae* (Mégnin, 1881) Blanchard, 1896. However, *Trichophyton Megnini* Blanchard, 1896, is the most familiar name for the group and is retained for the present.

This group differs only slightly from the "rubrum group," and contains a single species with numerous synonyms.

Trichophyton Megnini Blanchard, 1896.

The colony is cottony to velvety and white at first, but later becomes pale rose with the agar becoming wine red to violet in color due to the diffusible pigment.

Microscopically, microconidia are borne singly along the hyphae and rarely in clusters. Racquet hyphae, chlamydospores and small [illegible]

[illegible] onymy.—?*Epi*- [illegible] *roseum* Bodin, 1902; *Trichophyton rosaceum* Sabouraud, 1909; *Trichophyton vinosum* Sabouraud, 1910; ?*Achorion gallinae* Sabouraud, 1910

MICROSPORUM

(Gruby, 1843)

Cultures of *Microsporum* develop cottony, wooly, matted or powdery aerial mycelium varying in color from white, buff to deeper shades of brown.

Microscopically, the large (8 to 15 μ in width, 40 to 150 μ in length), multicelled, rough thick-walled, spindle-shaped macroconidia (fuseaux) immediately identify the genus; single-celled, small (3 to 6 μ), clavate microconidia are borne along the sides of the hyphae, sessile or on short sterigmata. Racquet hyphae, pectinate hyphae, nodular bodies and chlamydospores also are found. Only three species are to be found in this genus

1. *Microsporum Audouini* Gruby, 1843

The colony is slow growing, consisting of close matted, velvety aerial mycelium, light gray to brown in the center with radiating furrows (Fig. 120*A*.) The reverse of the colony is reddish-brown to orange in color.

Microscopically, a few large, multiseptate macroconidia, typical of the genus, are seen in primary cultures. These large, spindle-shaped conidia are never numerous in this species and soon disappear. (Fig 120*B*.) Microconidia borne laterally along the hyphae are clavate, single-celled and sessile or on short sterigmata Racquet mycelium, pectinate hyphae, nodular bodies and chlamydospores are found.

Microsporum Audouini Gruby, 1843. Synonymy.—*Trichophyton decalvans* Malmsten, 1848, *Microsporum villosum* Minne, 1907, *Microsporum umbonatum* Sabouraud, 1907, *Microsporum velveticum* Sabouraud, 1907, *Microsporum tardum* Sabouraud, 1910, *Microsporum tomentosum* Sabouraud, 1910, *Microsporum depauperatum* Guéguen, 1911

2. *Microsporum canis* Bodin, 1902.

The colony develops quickly with a cottony to wooly aerial mycelium which becomes powdery and buff to light brown in the center. (Fig. 121*A*.) The reverse of the colony is reddish-brown to orange in color.

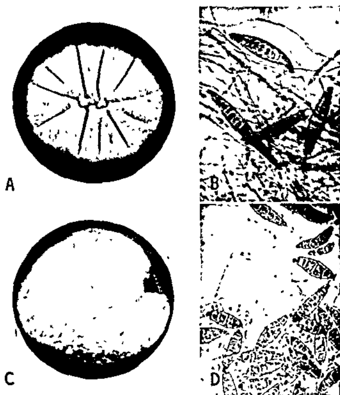


Fig 120—*A* *Microsporum Audouini* on Sabouraud's glucose agar *B* *M Audouini* multiseptate, spindle-shaped macroconidia × 250 *C* *M gypseum* on Sabouraud's glucose agar × 480 *D* *M gypseum* multiseptate, ellipsoid macroconidia × 250

Microscopically, numerous large, multiseptate, spindle-shaped, rough thick-walled macroconidia are seen (Fig. 121*B*.) In primary cultures, few small, single-celled, clavate microconidia are found

Racquet hyphae, pectinate hyphae, nodular bodies, chlamydospores and, rarely, coils are found.

Microsporum canis Bodin, 1902. Synonymy.—*Microsporum felineum* Mewborn, 1902; *Microsporum equinum* Guéguen, 1904, *Microsporum lanosum* Sabouraud, 1907; *Microsporum caninum* Sabouraud, 1908; *Sabouraudites lanatus* Le Basque, 1933; *Microsporum Stillianus* Benedek, 1937; *Microsporum aurantiacum* Conant, 1937; *Microsporum pseudolanosum* Conant, 1937; *Microsporum simiae* Conant, 1937; *Microsporum obesum* Conant, 1937.

3. *Microsporum gypseum* (Bodin) Guiart and Grigorakis, 1928.

The colony is fast growing, becoming powdery and buff to light brown in color. (Fig 120*C*.) Some strains develop a white, wooly aerial mycelium which later becomes powdery and light brown in the center with radiating furrows. Reverse of the colony is reddish-brown to orange in color.

[illegible] are found.

[illegible] and Grigorakis, 1928. [illegible]; *Microsporum fulvum* [illegible] Horta, 1911; *Microsporum scorteum* Priestley, 1914, *Microsporum xanthodes* Fisher, 1918.

EPIDERMOPHYTON

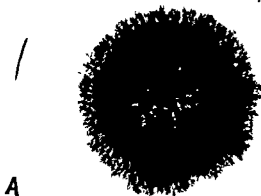
(Sabouraud, 1910)

In gross appearance, the cultures are characteristically velvety to powdery, with central radiating furrows, and greenish-yellow in color

Microscopically, the only conidia produced are the large, clavate, multiseptate, smooth thin-walled macroconidia. In the mycelium, chlamydospores and racquet hyphae are seen Only a single species is placed in this genus.

Epidermophyton floccosum (Harz) Langeron and Milochevitch, 1930.

The colony is at first white and granular with a small central tuft of mycelium. Later, the growth becomes velvety to powdery, with numerous radiating furrows, and greenish-yellow in color White, sterile (pleomorphic) aerial mycelium develops in about 3 weeks and spreads over the colony (Fig. 122*A*)





121 —*A* *Microsporum canis* on Sabouraud's glucose agar *B* *M canis* multiseptate, spindle-shaped macroconidia × 480

Microscopically, the large, clavate, multiseptate, smooth thin-walled macroconidia identify the fungus. Such macroconidia are borne singly from the hyphae or in typical clusters. (Fig. 122*B*.) No microconidia are developed. Chlamydospores are abundant in old cultures.

Epidermophyton floccosum (Harz) Langeron and Milochevitch, 1930. Synonymy.—*Trichothecium floccosum* Harz, 1870; *Acrothecium floccosum* Harz, 1871; *Trichophyton intertriginis* Sabouraud, 1905; *Trichophyton inguinale* Sabouraud, 1907; *Trichophyton cruris* Castellani, 1908; *Epidermophyton inguinale* Sabouraud, 1910; *Epidermophyton cruris* Castellani and Chalmers, 1910; *Epidermophyton plicarum* Nicolau, 1913; *Epidermophyton clypeiforme* MacCarthy, 1925.

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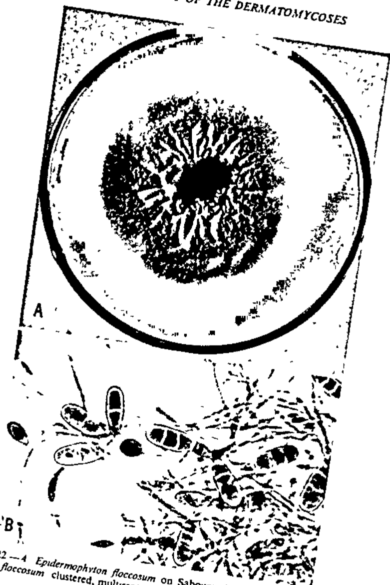
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2 —A *Epidermophyton floccosum* on Sabouraud's glucose agar *B E. floccosum* clustered, multiseptate, clavate macroconidia × 600

Chapter XIX

PIEDRA

(*Black Piedra, White Piedra, Tinea Nodosa, Piedra Nostros, Trichomycosis Nodularis, Trichomycosis Nodosa, Chignon's Disease, Beigel's Disease*)

Definition.—Piedra is a fungus infection of the hair, characterized by the presence of stony hard nodules along the hair shafts and caused either by *Piedraia Hortai* (black piedra) or *Trichosporon Beigelii* (white piedra).

Geographic Distribution.—"Black piedra" is found in South America (Brazil, Paraguay, Colombia, Argentina, Uruguay, Dutch Guiana, British Venezuela), Java and Cochinchina. (Fig. 123.) "White piedra" is found in South America (Brazil, Paraguay, Colombia, Argentina, Uruguay, Venezuela), Central Europe, England and Japan (Fig. 124)

SYMPTOMATOLOGY

Piedra, which is limited to the hairs of the scalp, beard and mustache, causes no discomfort to the patient since only the shafts of the hair are involved. The concretions are firmly adherent to the hair shaft and may be so small that they can be seen only with the microscope. The larger nodules are visible, easily palpated and cause a gritty feeling when the hair is drawn through the fingers A sharp metallic sound is produced when the hair is combed

"Black piedra," which is confined almost exclusively to certain tropical regions, is endemic in certain areas, especially those with abundant rainfall. *Piedraia Hortai* affects only the hairs of the scalp where it invades beneath the cuticle, then expands and ruptures to spread around the hair shaft, forming dark brown and black nodules. (Fig. 125.)

The rarer "white piedra" occurs sporadically in the temperate regions but occasionally can be found in the tropics The infection occurs on the hair of the beard and mustache, the nodules are light brown in color and less firmly adherent to the hair shaft It is thought that *T Beigelii* infection can occur only in a previously damaged hair.

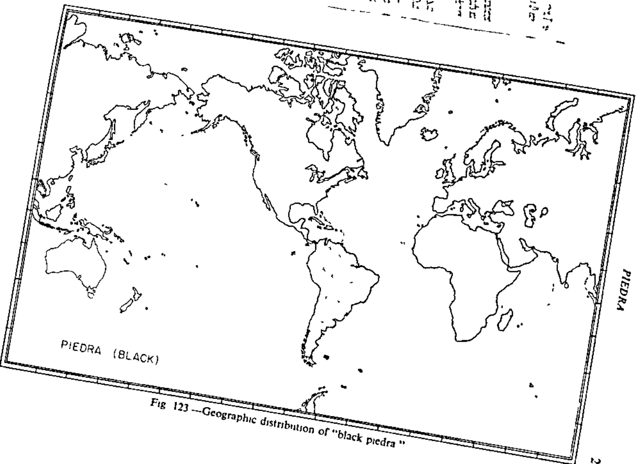


Fig 123 —Geographic distribution of "black piedra"

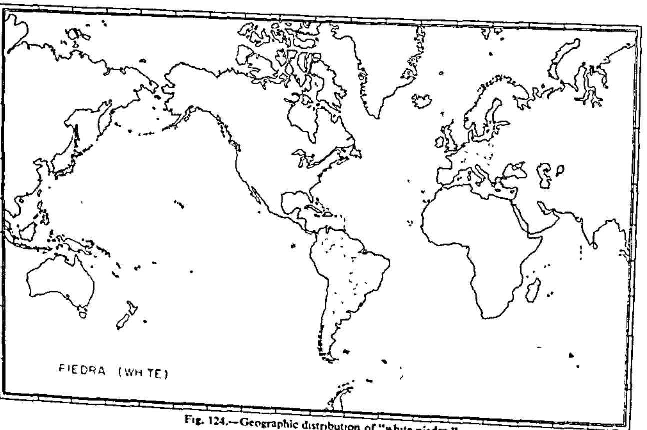


Fig. 124.— Geographic distribution of "white piedra."



Fig. 125.—Black piedra *A* Infection starting under the cuticle × 177. *B* Fungus beginning to surround hair × 177 *C* Hair encircled with black nodule of *Piedraia Hortai* × 177

MYCOLOGY

Although several species of fungi have been described as causing piedra, the consensus is that only 2 fungi need be considered: *Piedraia Hortai* (Brumpt) Fonseca and Leão, 1928, and *Trichosporon Beigelii* (Rabenhorst) Vuillemin, 1902.

Direct Examination.—Infected hairs should be cut off and examined in a 10 per cent potassium hydroxide preparation.

The nodules caused by *P. Hortai* vary in size and are discrete with normal hair between them. The nodules consist of a tightly packed stroma of dark brown, dichotomously branched hyphae, 4 to 8 μ in diameter, which seem to be held together by a cement-like material. The hyphae have numerous septations at such close intervals that the chains of stout, thick-walled cells resemble arthrospores. A crushed nodule reveals numerous asci containing 2 to 8 single-celled, fusiform, slightly curved ascospores with a single polar filament at each end.

The nodules caused by *T. Beigelii* also are variable in size but are softer and more easily detached from the hair. The nodules are not as discrete as those of "black piedra," and the transparent greenish-tinged mycelial mass is seen to extend along the hair as a sheath. The infected hair may show only a raised cuticle, but more often it is altered severely, producing trichorrhexis or trichoptilosis. The hyphae tend to lie perpendicular to the surface of the hair and segment into round, oval or rectangular cells, 2 to 4 μ in diameter but occasionally as large as 8 μ. Budding cells (blastospores) also are seen in the mycelial mass which contains no asci. Gram-positive cocci frequently are found in the fungus mass.

Cultures.—*P. Hortai* grown on Sabouraud's medium at room temperature develops as adherent greenish-black to black colonies which are elevated in the center or are flat, glabrous or smooth to cerebriform. Microscopic examination shows dark, thick-walled, closely septate hyphae containing numerous chlamydospores or swollen, irregularly shaped cells. Asci and ascospores develop occasionally in cultures and resemble those seen on direct examination of infected hairs.

Colonies of *T. Beigelii* on Sabouraud's medium at room temperature develop rapidly and appear first as a cream-colored, slimy growth which is soft in consistency. Later, the colony becomes finely wrinkled and more adherent to the agar, the center becomes heaped and the color becomes a little darker (Fig. 126.)

Mycologic Diagnosis.—The nodules of piedra can be distinguished from those of axillary trichomycosis by direct examination since the hyphae in piedra are wider (2 to 4 μ) than those seen in trichomycosis (1 μ or less)



Fig 126 —*Trichosporon Beigelii* Culture on Sabouraud s glucose agar, thirty-five days, at room temperature

Piedraia Hortai (Brumpt) Fonseca and Leão, 1928 Synonymy.—*Trichosporum Hortai* Brumpt, 1913, *Trichosporum paraguayo* Delamare and Gatti, 1928, *Piedraia Sarmentoi* Pereira, 1930; *Piedraia venezuelensis* Brumpt and Langeron, 1934, *Piedraia surinamensis* Dodge, 1935, *Piedraia javanica* Boedijn and Verbunt, 1938

Trichosporon Beigelii (Rabenhorst) Vuillemin, 1902. Synonymy.—*Pleurococcus Beigelli* Rabenhorst, 1867; *Trichosporon ovoides* Behrend, 1890; *Trichosporon giganteum* Unna, 1895; *Trichosporon cerebriforme* (Kambayashi) Ota, 1928; *Trichosporon granulosum* (Kambayashi) Ota, 1928; *Trichosporon humakuaquensis* Mazza and Niño, 1933; *Piedraia colombiana* Dodge, 1935; *Trichosporon minor* Leão, 1940.

DIFFERENTIAL DIAGNOSIS

Piedra is differentiated from trichomycosis nodosa, trichorrhexis nodosa and the nits of pediculosis capitis by microscopic examination of the nodules.

PROGNOSIS

The lesions usually can be cured by local treatment, but re-infection may occur.

TREATMENT

Vigorous shampooing daily should be followed by application of *a solution of bichloride of mercury (1:2000). The beard and mustache* should be shaved and bichloride of mercury solution or ammoniated mercury ointment (3 per cent) applied.

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Chapter XX

TRICHOMYCOSIS AXILLARIS

(*Lepothrix, Trichomycosis Nodosa, Trichomycosis Palmellina, Trichomycosis Chromatica, Trichonocardiasis Axillaris*)

Definition.—Trichomycosis axillaris is a fungus infection of the axillary and pubic hairs, caused by *Nocardia tenuis* (Castellani, 1911) and characterized by the development of yellow (flava), red (rubra) or black (nigra) concretions surrounding the hair shaft.

Geographic Distribution.—The disease is more prevalent in the temperate climate than is generally realized, but it is more widespread in the tropics where heat and moisture favor the growth of the fungus

SYMPTOMATOLOGY

The infection involves only the shafts of the hairs in the axillary and pubic regions. The nodules are yellow, red or black and are discrete and scattered along the hair shaft, or they form a continuous sheath along the hair. (Fig 127) The concretions are hard and firmly adherent and may include cortical fibers since the cortex of the hair is invaded by the fungus The hair appears lusterless and brittle and breaks easily. The infection does not extend to the roots or involve the surrounding skin The most common type of nodule is yellow in color, the red and black varieties following in the order named. The red and black colors are produced by associated pigment-producing bacteria.

MYCOLOGY

Trichomycosis axillaris is caused by *N tenuis* (Castellani, 1911) The fungus is said to be the only organism found in nodules of the yellow or "flava" variety The fungus is found associated with a red pigment-producing coccus in the red or "rubra" variety and with a black pigment-producing coccus in the black or "nigra" variety

Direct Examination.—Infected hairs should be obtained for microscopic examination and placed on a slide in a drop of 10 per cent potassium hydroxide and examined under a cover glass The preparation may be heated gently for clearing

The nodules on the hairs (Fig 128) are seen to be composed of delicate, short, branching mycelial elements, 1 μ or less in diameter

Trichosporon Beigelii (Rabenhorst) Vuillemin, 1902. Synonymy.—*Pleurococcus Beigelii* Rabenhorst, 1867; *Trichosporon ovoides* Behrend, 1890; *Trichosporon giganteum* Unna, 1895; *Trichosporon cerebriforme* (Kambayashi) Ota, 1928; *Trichosporon granulosum* (Kambayashi) Ota, 1928; *Trichosporon humakuaquensis* Mazza and Niño, 1933; *Piedraia colombiana* Dodge, 1935; *Trichosporon minor* Leão, 1940.

DIFFERENTIAL DIAGNOSIS

Piedra is differentiated from trichomycosis nodosa, trichorrhexis nodosa and the nits of pediculosis capitis by microscopic examination of the nodules.

PROGNOSIS

The lesions usually can be cured by local treatment, but re-infection may occur.

TREATMENT

Vigorous shampooing daily should be followed by application of a solution of bichloride of mercury (1:2000). The beard and mustache should be shaved and bichloride of mercury solution or ammoniated mercury ointment (3 per cent) applied.

REFERENCES

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Chapter XX

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Direct Examination.—Infected hairs should be obtained for microscopic examination and placed on a slide in a drop of 10 per cent potassium hydroxide and examined under a cover glass. The preparation may be heated gently for clearing

The nodules on the hairs (Fig 128) are seen to be composed of delicate, short, branching mycelial elements, 1 μ or less in diameter

Trichosporon Beigelii (Rabenhorst) Vuillemin, 1902. Synonymy.—*Pleurococcus Beigelli* Rabenhorst, 1867; *Trichosporon ovoides* Behrend, 1890; *Trichosporon giganteum* Unna, 1895; *Trichosporon cerebriforme* (Kambayashi) Ota, 1928; *Trichosporon granulosum* (Kambayashi) Ota, 1928; *Trichosporon humakuaquensis* Mazza and Niño, 1933; *Piedraia colombiana* Dodge, 1935; *Trichosporon minor* Leão, 1940.

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Piedra is differentiated from trichomycosis nodosa, trichorrhexis nodosa and the nits of pediculosis capitis by microscopic examination of the nodules.

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The lesions usually can be cured by local treatment, but re-infection may occur.

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Pereira Culturas da piedra brasileira Piedraia Sarmentoi n sp Rev. Med Cir do Brasil, *38* 49, 1929 *50* 51, 1930.

When crushed, the short, almost bacillary forms are seen to be embedded in mucilaginous material. The red and black varieties show numerous clumps of cocci mixed with the bacillary forms of the fungus.

Cultures.—*N. tenuis* is said to produce translucent colonies on ascitic fluid agar. *Micrococcus Castellani* and *M. nigrescens* are the

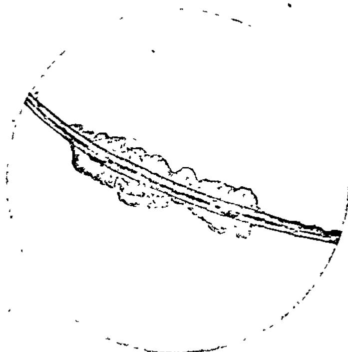


Fig. 128.—Nodule of trichomycosis axillaris Potassium hydroxide preparation Low power

names usually applied to the pigment-producing cocci found in the red and bl [illegible]

[illegible] or bacillary forms [illegible] nodules readily differentiate trichomycosis from piedra, in which can be found the characteristic wide, septate, thick-walled mycelial elements



Fig 127 —Trichomycosis axillaris demonstrating waxy fungus sheaths surrounding the hairs

When crushed, the short, almost bacillary forms are seen to be embedded in mucilaginous material. The red and black varieties show numerous clumps of cocci mixed with the bacillary forms of the fungus.

Cultures.—*N. tenuis* is said to produce translucent colonies on ascitic fluid agar. *Micrococcus Castellani* and *M. nigrescens* are the

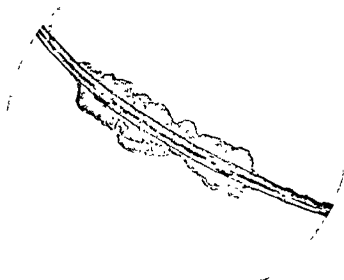


Fig. 128.—Nodule of trichomycosis axillaris. Potassium hydroxide preparation. Low power.

names usually applied to the pigment-producing cocci found in the red and black varieties respectively.

Mycologic Diagnosis.—The delicate mycelial or bacillary forms embedded in the mucilaginous material of the nodules readily differentiate trichomycosis from piedra, in which can be found the characteristic wide, septate, thick-walled mycelial elements.

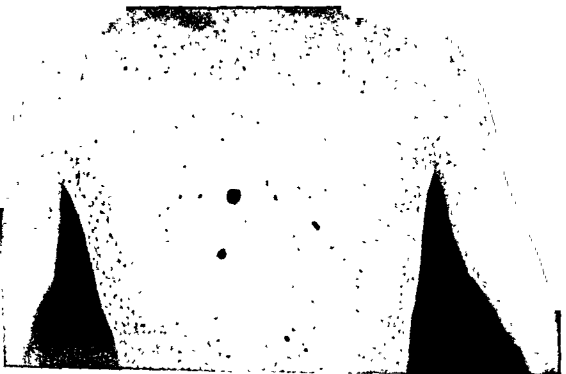


Fig. 129.—Generalized tinea versicolor demonstrating superficial brownish, scaling appearance.

Direct Examination.—Scales should be scraped from the fawn-colored macules with a scalpel and mounted directly on a slide in a drop of 10 per cent potassium hydroxide. The preparation should be covered with a cover glass and gently heated over a low flame for clearing. The scales are usually thin enough to permit direct examination in a drop of methylene blue. The fungus is seen as clusters of thick-walled, round and budding forms (3 to 8 μ in diameter) surrounded by short, straight and angular fragments of mycelium. (Fig 130)

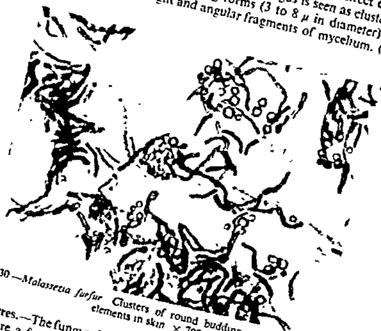


Fig. 130—*Malassezia furfur* Clusters of round budding cells and mycelial elements in skin × 700

Cultures.—The fungi referred to above probably are contaminants There are a few reports in the literature in which positive cultures have been obtained by inoculating material from the lesions onto a variety of media, but failure to obtain growth is such a constant finding that routine cultures are not made

Mycologic Diagnosis.—The characteristic arrangement of the round budding forms and mycelial fragments in potassium hydroxide preparations of the skin lesions is diagnostic for this disease

Malassezia furfur (Robin) Baillon, 1889 Synonymy.—*Microsporon furfur* Robin, 1853, *Malassezia Macfadyeni* Castellani, 1908, *Malassezia tropica* Castellani, 1919.



Fig 131.—Tinea versicolor of neck and face

DIFFERENTIAL DIAGNOSIS

The brownish-red, irregularly distributed, furfuraceous patches, with or without achromia, suggest the diagnosis, which can be confirmed easily by microscopic examination. The infection must be differentiated from seborrheic dermatitis, erythrasma, secondary syphilis, pityriasis rosea, cholasma, vitiligo, achromia parasitica of Pardo-Castello and Dominguez and tinea corporis

PROGNOSIS

The prognosis is good if all areas are treated carefully and therapy continued for at least two weeks after the disappearance of lesions as checked by the Wood's light.

TREATMENT

Hot soap baths should be taken twice daily, followed by vigorous scrubbing of the skin with a coarse towel and the application of an aqueous solution of sodium hyposulfite (20 per cent) ... tartaric acid (3 per cent) also helps to ... Vineger ... f ointment ... may be ... field's o... boiling a... ...s and linen ... ...ection should be avoided by

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has been paid to the role played by *pathogenic bacteria* which frequently are found in such infe[illegible] the presence [illegible] utes to the mai[illegible] of the [illegible]

[illegible] of such a preparation under a cover glass *reveals strands of* mycelium, spores and the characteristic swollen *conidiophores of* fungi such as *Aspergillus*. (Fig. 133)

Cultures.—The material from the ear should be planted *on* Sabouraud's glucose agar slants and the cultures held for at least 2 weeks before discarding since most of the saprophytic fungi should develop within this time. Cultures for bacteria also should be *made* by streaking blood agar plates.

Specific identification of the fungus presents a problem because of the wide variety of organism that may be isolated. In the majority of cases, the fungus will prove to be *Aspergillus, Penicillium, Mucor* or *Rhizopus*. The cultural and microscopic characteristics of such fungi may be found in the section on contaminants.

Mycologic Diagnosis.—The diagnosis is established by the demonstration of mycelium and spores in fresh preparations of material from the ear canal.

DIFFERENTIAL DIAGNOSIS

The diagnosis is suspected from the clinical appearance of the infection and is confirmed easily by microscopic examination *Streptococcus* dermatitis of the ear, as described by Mitchell, may be confusing. Seborrheic dermatitis of the ear canal usually is associated with dermatitis elsewhere on the body. Impetigo contagiosa, furunculosis, contact dermatitis (nail polish) and allergic affections must be considered.

PROGNOSIS

Occasionally, the lesions are very resistant to all forms of treatment but, in general, the prognosis is considered fair to good if the diagnosis is made promptly and treatment is applied diligently.

TREATMENT

The ear should be kept dry, and swimming must be prohibited unless proper precautions are taken to avoid getting water into the ear canal. All cerumen should be removed and the canal kept clean

by treatment directed toward the removal of the superficial layers of epithelium containing the fungus. Included among the many medications recommended are: gentian violet (1 per cent) in alcohol (20 per cent); salicylic acid (3 per cent) in alcohol (70 per cent) and metacresyl acetate (cresatin). It has come to our attention that an entirely new method of treatment is being used with great success by physicians in the Army.

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Chapter XXIII

ERYTHRASMA

Definition.—Erythrasma is a chronic fungus infection of the stratum corneum, caused by *Nocardia minutissima* (Buchardt) Verdun, 1912, characterized by superficial lesions in the axillae and genitocrural regions but occasionally involving other intertriginous areas.

Geographic Distribution.—The disease occurs throughout the world, but is found more commonly in the tropics and Europe than in the United States.

SYMPTOMATOLOGY

The lesions appear as punctate to palm-sized, well-circumscribed, maculopapular areas which vary from light brown to reddish or reddish-brown in color. The color of the lesion is dependent apparently upon its age and upon the underlying pigmentation of the skin

The spreading of an infected area is characterized by the development of a serpiginous erythematous border, the lesion is not elevated

and there is no tendency to vesiculation. (Fig 134) The surface of the lesion is covered with small, furfuraceous scales and feels greasy

The infection occurs most often in young men and causes no symptoms unless eczematous changes develop under conditions of excessive perspiration or maceration

MYCOLOGY

Although cultures have been obtained, the procedure is difficult and the diagnosis can be established by direct microscopic examination of the infected skin.

Direct Examination.—Bits of skin should be scraped from the infected areas by means of a scalpel or the edge of a microscopic slide. Such materials should be defatted by placing them in a drop of ether and the ether allowed to evaporate. The scales should be covered with methylene blue or lactophenol cotton blue and examined under a cover glass with the oil immersion objective of the microscope. If the fungus is not readily seen and lactophenol cotton blue has been used, the slide may be heated gently over a low flame and the cover glass pressed to thin out the preparation

The fungus appears as short, delicate, branching filaments, 1 μ or less in diameter, which are readily broken up into smaller bacillary or coccoid forms (Fig 135) Such forms may be difficult to find and a careful search of the material may be necessary before the fungus can be demonstrated.

Cultures.—Culturing of the fungus is not a routine procedure. The fungus has been named *Nocardia (Actinomyces)* because of its appearance in the skin.

Mycologic Diagnosis.—The morphologic characteristics of the fungus as seen in microscopic preparations readily distinguish it from species of *Trichophyton* or *Epidermophyton floccosum* which can produce lesions in the axillae and genitocrural regions or species of *Candida* which produce lesions in intertriginous areas

Nocardia minutissima (Buchardt) Verdun, 1912 **Synonymy.**—*Microsporon minutissimum* Buchardt, 1859, *Sporotrichum minutissimum* Saccardo, 1886; *Microsporoides minutissimus* Neveu-Lemaire, 1906, *Discomyces minutissimus* Verdun, 1907, *Oospora minutissima* Ridet, 1911, *Actinomyces minutissimus* Brumpt, 1927

DIFFERENTIAL DIAGNOSIS

The appearance of chronic non-inflammatory, brownish-yellow lesions in the axillae, genitocrural regions or intertriginous areas sug-



Fig. 134.—Erythrasma of axilla. Note absence of reaction and superficial character.

gests erythrasma. Microscopic examination of scales in 10 per cent potassium hydroxide in which the minute organisms may be seen definitely establishes the diagnosis. Tinea versicolor is not limited to the intertriginous areas and fluorescence can be demonstrated under the Wood's light. Tinea cruris, other mycotic lesions and contact dermatitis show more acute inflammatory changes with vesicle formation.

PROGNOSIS

The prognosis is good if all areas involved are treated carefully.



Fig 135.—Erythrasma Small bacillary forms seen in skin scrapings × 1630

TREATMENT

[illegible]

(10 per cent) in alcohol may be sponged on twice daily. All members of the family should be treated, and all linens and clothing should [illegible] laundered

Chapter XXIV

FUNDAMENTALS OF ELEMENTARY MYCOLOGY

Most technicians and many physicians become confused and discouraged in their attempts to study the fungi because of the variation in gross colonies, the multiplicity of microscopic structures and unfamiliar nomenclature. Such difficulties, however, are more psychological than real, and when a few basic concepts and a few new names have been mastered, the identification of fungi becomes easier and more rapid than that of ordinary pathogenic bacteria.

Fungi reproduce by spores of one type or another. On a suitable substrate, a fungus spore enlarges somewhat and germinates, sending out one or more tube-like processes called GERM TUBES. Such germ tubes elongate by growth at the distal end and become long filaments which eventually branch; each filament is called a HYPHA (pl. HYPHAE).

[illegible]

known as SEPTATE HYPHAE. Some fungi, however, do not develop septations in the hyphae and are said to be NON-SEPTATE. Non-septate *hyphae allow the nucleated protoplasm to flow uninterruptedly* throughout the tubes and are described as being COENOCYTIC.

As the hyphae continue to grow and branch, there soon develops *a mat of growth called the MYCELIUM (pl. MYCELIA).* That part of the mycelium which penetrates into the substrate and absorbs food for further growth is known as the VEGETATIVE MYCELIUM, that part of the growth which projects above the surface of the substrate is called the AERIAL MYCELIUM. From the aerial mycelium spores are produced in very characteristic ways, and these spores act as the propagating structures which, on dispersal to new substrates, germinate and form new growths. An aerial mycelium developing the reproductive spores of various kinds is referred to as REPRODUCTIVE MYCELIUM. The rudimentary type of plant structure described above is known as a [illegible] ore [illegible] um

THALLOPHYTA which is a large division of the plant kingdom

Another group of simple thallus plants, the ALGAE, are also placed in this phylum but, unlike the fungi, they contain chlorophyl which allows them to manufacture their own food. Fungi lack this substance and are either saprophytic or parasitic.

[illegible]

bacteria, in which class are placed the human pathogenic fungi *Actinomyces* and *Nocardia*, and (2) the MYXOMYCETES, or slime molds, none of which is pathogenic for man

The Eumycetes, or true fungi, are divided into four classes: the PHYCOMYCETES, ASCOMYCETES, BASIDIOMYCETES and FUNGI IMPERFECTI. (Table V.) These four classes of fungi are identified and classified by the type of colony produced, the presence or absence of mycelium, the type of mycelium, the character of the spores (size, shape, color, and so on) and the method of spore development, whether in definite fruiting bodies or produced in, on or from the mycelium

TABLE V. THALLOPHYTA

Thallus-bodied Plants Which Lack Roots, Stems and Leaves

ALGAE	FUNGI (MYCETES)
Contain chlorophyl, synthesize food from carbon dioxide and water with aid of sunlight.	Do not contain chlorophyl, are saprophytic or parasitic A PSEUDOMYCETES 1. SCHIZOMYCETES 2 MYXOMYCETES B EUMYCETES a) Non-septate mycelium 1 PHYCOMYCETES b) Septate mycelium 1 ASCOMYCETES 2 BASIDIOMYCETES 3. FUNGI IMPERFECTI

The simplest and most primitive types of colony and spore formation a re found in the unicellular fungi, *Cryptococcus* and *Saccharomyces*. Both fungi, when grown on glucose agar at room or incubator temperature, develop soft colonies with a consistency about like that of a colony of *Staphylococcus* Microscopic examination of *Cryptococcus* in an aqueous preparation reveals the presence of round or oval (egg-shaped), thin-walled cells, 3 to 6 μ in diameter. Instead of

germinating to form germ tubes and mycelium, the cells reproduce only by budding. As the buds break off the parent cell, they enlarge and propagate likewise by budding. Such a simple type of spore formation by budding is ASEXUAL (no fusion of nuclei takes place in the formation of the spore) and the spore is called a BLASTOSPORE. (*Fig. 136A.*)

Microscopic examination of colonies of *Saccharomyces* also reveals round or oval cells which reproduce by budding but, in addition, when conditions of growth become favorable for their production also develop spores *inside* of somewhat enlarged cells. Such spores usually are 8 in number and are called SEXUAL SPORES because they

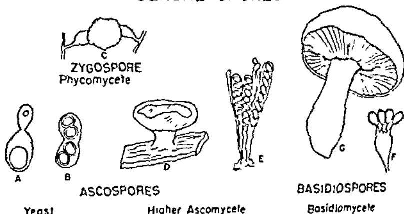


Fig. 136.—Various types of sexual spores.

develop as a result of a primary nuclear fusion with reduction in chromosome number during their formation. The cell or sac which contains the spores is called an ASCUS and the spores are referred to as ASCOSPORES (Fig 136*B*) Such spores allow this fungus to be placed in the *Ascomycetes* which are characterized by the formation of ascospores (endospores in a sac). *Saccharomyces* is a primitive member of this class, however, because it is a unicellular fungus and does not produce mycelium. The pasty type of colony produced by unicellular fungi which lack mycelium and reproduce by blastospores, and occasionally by ascospores, is known as a YEAST colony.

A further step in the development of fungi from the unicellular

type which reproduces only by budding may be exemplified by species of the genus *Candida* (*Monilia*), which also produces soft, white colonies on the surface of glucose agar at room or incubator temperature. Microscopic examination of the surface growth reveals oval, thin-walled cells which reproduce by budding. Examination of the growth in the agar, however, shows that the buds elongate and do not become detached from the parent cells and by repeated budding form a branching network made up of long chains of the attached cells. On close examination it is seen that the filaments are not of equal diameter along their length but are constricted at the points of septation, which shows that the filaments are composed of elongated budding cells which have failed to detach Such hyphae are calle[illegible]

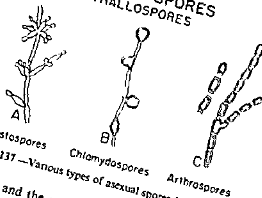


Fig 137 —Various types of asexual spores (thallospores)

PSEUDOHYPHAE and the mycelium resulting from their formation is known as a PSEUDOMYCELIUM (Fig 137*A*) The soft type of colony which is produced by unicellular budding fungi which also have the ability to form pseudomycelium is known as a YEASTLIKE colony.

The production of true mycelium by spores which germinate to form branching hyphae results in the formation of a FILAMENTOUS colony. This type of colony usually develops an aerial mycelium that appears cottony, wooly, powdery, granular, and so on, and is familiar to most people as the type of growth associated with "[illegible]

The type of mycelium found in the filamentous colony [illegible] importance in distinguishing the PHYCOMYCETES from all [illegible] of fungi. In this class the hyphae are NON-SEPTATE and [illegible]

Septa sometimes occur, however, in old cultures and where the spore producing structures are cut off. The PHYCOMYCETES are further differentiated from the other classes by producing asexual spores inside of swollen structures which are developed on the ends of branches. The terminal swollen structure is called a SPORANGIUM (pl. SPORANGIA) and the spores contained inside of such a sporangium are referred to as SPORANGIOSPORES. (Fig. 138*A*.) The branch or hypha from which the sporangium is developed is called a SPORANGIOPHORE. For propagation, the sporangial wall breaks and the spores are freed to find

ASEXUAL SPORES
CONIDIA

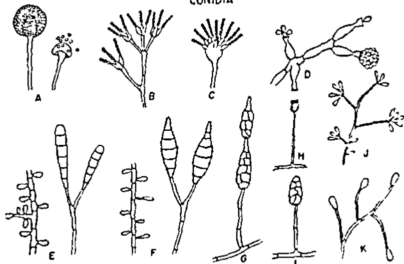


Fig. 138 —Various types of asexual spores (conidia)

suitable substrates where they germinate to form new colonies. Two type [illegible] within the [illegible] fungi, [illegible] 136*C*.) *Mucor* and *Rhizopus* are the familiar fungi developing these structures. The second type of sexual spore is developed by the fertilization of the contents of a special female structure on the mycelium by the nucleus of a male structure developed close by. The spore

resulting from this process of fertilization is called an OOSPORE and the structure which contains it, an OOSPHERE. The PHYCOMYCETES are distinguished from the other classes, therefore, by the non-septate hyphae, by the development of asexual spores, sporangiospores, in sporangia and by the development of sexual spores known as zygospores and oospores. All other filamentous fungi are characterized by septate mycelium, and the various classes are distinguished from each other by the type of spores which they produce.

The ASCOMYCETES are characterized by the formation of sexual spores (ascospores) within a sac (ascus) *Saccharomyces*, as we have already mentioned, is the simplest member of this class It is a unicellular fungus, lacks mycelium and is placed here only because of the development of 1 to 8 ascospores within single, round, exposed asci. In the majority of fungi belonging to this class, however, the organisms develop septate mycelia, are multicellular and several club-shaped asci are enclosed in a definite fruiting body called an ASCOCARP. The ascocarp varies greatly in size and shape A closed ascocarp which is spherical or flask-shaped when mature is called a PERITHECIUM, an ascocarp which is open and saucer or cup shaped when mature is called an APOTHECIUM (Fig 136*D*.) The morphologic character of these ascocarps serves to divide the ASCOMYCETES into well-defined groups. the PLECTOMYCETES, which lack an ascocarp, the asci being irregularly arranged in the mycelial mass, the DISCOMYCETES, which develop an apothecium, and the PYRENOMYCETES, which develop a perithecium Many of the ASCOMYCETES, in addition to the sexual phase typified by the ascospore, have an asexual phase typified by ASEXUAL SPORES The asexual spores are of various shapes and sizes and are developed from the mycelium. Such a spore is called a CONIDIUM (pl CONIDIA), and the specialized branches which bear them are referred to as CONIDIOPHORES The ASCOMYCETES are distinguished from other fungi, therefore, by the development of sexual spores (ascospores) in a sac-like structure, the ascus, and asexual spores (conidia) from the mycelium on specialized structures, the conidiophores.

The BASIDIOMYCETES develop spores, typically 4 in number, from the ends of club-shaped structures Such a structure, because of its shape, is called a BASIDIUM (pl BASIDIA) and the spores are referred to as BASIDIOSPORES (Fig 136*F*) Study of the nuclear behavior during the development of the basidiospores has shown that they are sexual spores. The more familiar forms in this class are the mushrooms, toadstools or the large bracket fungi seen growing from the limbs or

trunks of trees. In such forms the mycelium is organized into dense layers which make up the large body of the plant. (Fig. 136G.) The Rusts and Smuts, which cause great damage to cereal crops, are included among the BASIDIOMYCETES, and there are poisonous species which, when mistaken for edible mushrooms, cause serious and sometimes fatal poisoning of man. The BASIDIOMYCETES differ from the other fungi by the exogenous development of sexual spores, basidiospores, on the end of a club-shaped structure, the *basidium*.

The mode of development and the accompanying structure of the sexual stage of spore production in the PHYCOMYCETES, ASCOMYCETES and BASIDIOMYCETES remain fairly constant in their morphologic characters and can be used to form a basis for the classification of the fungi in these classes.

Included in the FUNGI IMPERFECTI are those organisms which do not have a sexual stage and cannot be placed among the previously described classes, and this class also contains the asexual conidial stages of the ASCOMYCETES. Occasionally, however, some of the fungi which have been described as producing only asexual spores have been proved to have an ascospore stage when studied further. Such studies have suggested that the perfect or sexual stage may be found in many fungi now thought to have only an asexual life cycle. The so-called incompletely known fungi have been placed, therefore, in the class FUNGI IMPERFECTI.

Because the imperfect fungi are classified entirely by the type of asexual spore produced in, on or from the mycelium, they present many difficulties from the point of view of classification. The conidial structures do not remain constant but vary considerably, depending upon the strain studied, the type of medium used and the temperature at which they are grown. Also, a pure culture of a single fungus may contain several spore types which would allow it to be placed in two or more different genera Since such fungi lack the constant morphologic characters found in those having a perfect or sexual stage, a scheme of classification based on phylogeny cannot be used, and the organisms are placed in so-called "form-genera" which include fungi which are morphologically similar but which may have been derived from different genetic types. Any classification of such fungi can serve only to catalogue the different forms to promote some means of identification.

One order of the FUNGI IMPERFECTI, the HYPHOMYCETALES, is divided into four families, but only two of these are of importance to

the worker in the bacteriology laboratory: the colorless or light-colored fungi, MUCEDINACEAE, and the dark brown or black fungi, DEMATIACEAE. The HYPHOMYCETALES, therefore, are divided roughly into two groups based on the color of their mycelium and are further subdivided depending upon the type of spore produced (single-celled, two-celled, and so on, and the shape of the spores) and the type of conidiophore on which the spores are borne (distinct from the mycelium or hardly distinguishable from the mycelium). For a complete system of classification of these fungi, those of Saccardo and Clements and Shear (see literature) are most complete.

The asexual spores, upon which the classification and identification of the FUNGI IMPERFECTI are based, are of two major types: the so-called THALLOSPORES and CONIDIA. The thallospores are those reproductive spores which are formed by the thallus or mycelium. That type of spore which is formed by a budding process from the cells of the mycelium is called a BLASTOSPORE. (Fig 137A.) The simplest type of mycelium, unicellular, is that found in *Cryptococcus* which has been described. In the genus *Candida* (*Monilia*), the various species produce a pseudomycelium by the formation of elongate buds which fail to detach. Buds are developed which serve as spores at the points of constriction of the cells in the pseudohyphae. Such buds also are considered to be blastospores because they were derived also from the thallus or mycelium. Also in this group, one species, *Candida albicans*, converts the terminal cells of the pseudohyphae into round, thick-walled, resting spores, called CHLAMYDOSPORES (Fig 73B), which represent a second type of thallospore. Among the truly filamentous fungi, cells of the mycelium may concentrate their protoplasm, enlarge to become greater than the diameter of the hyphae in which they are formed and develop a thick wall, spores of which also are called chlamydospores. Chlamydospores formed in the hypha are said to be INTERCALARY CHLAMYDOSPORES, those formed on the end of the hypha are called TERMINAL CHLAMYDOSPORES, those formed on the side of the hypha are said to be LATERAL CHLAMYDOSPORES (Fig 137B.) Such thick-walled, resting spores (chalmydospores) are produced by the majority of fungi and are supposed to carry the fungus through unfavorable environmental conditions, and when conditions for growth become favorable, they germinate by one or more germ tubes and produce a new growth.

A third type of thallospore is formed by segmentation of the hyphae which results in the cutting off of rectangular, somewhat thick-walled cells. Such a type of cell is called an ARTHROSPORE. (Fig. 137C.) Fungi

[illegible]

greatly in their size, shape, number of septations, color, and so on, as do the conidiophores. Such differences serve to separate the numerous genera and species among the FUNGI IMPERFECTI, and the fungi can be identified only by a careful microscopic examination of these structures.

Conidia which are small and single-celled are called MICROCONIDIA (Fig. 138*E, F*) in contrast to conidia which are large, usually multicelled and called MACROCONIDIA. (Fig. 138*E, F, G, I.*) The microconidia may be round (SPHERICAL), egg-shaped (ELLIPTICAL or ELLIPSOID, OVAL or OVOID), pear-shaped (PYRIFORM) or club-shaped (CLAVATE.) The macroconidia may be divided into two or more cells by transverse septations and may appear spindle-shaped (FUSIFORM) or club-shaped (CLAVATE). A macroconidium that is divided by both transverse and longitudinal septations is called MURIFORM. (Fig. 138*G*, [illegible]

(thyrse, French). (Fig 138*E, F.*) Conidia also may be produced later- [illegible]

phores, they are said to be PEDUNCULATE or PEDICELLATE and the conidiophore may be referred to as a PEDICLE. (Fig 138*F*) On more highly developed conidiophores, the conidia may be produced singly, in globose clusters, in loose clusters or in chain formation (Fig 138*B, C, H, J, K*)

Highly developed conidiophores usually have characteristic shapes and the conidia are developed from them in such a definite manner that identification often can be made on the structure of the conidiophore. In *Aspergillus*, for example, the conidiophore is swollen at the end and over the surface of this swollen area several small, flask-shaped structures are produced. The tips of these flask-shaped structures are growing points and the conidia are cut off successively As the conidia are pushed ahead from the tip of the flask-shaped structures, they remain attached and appear in chain formation The swollen portion of the conidiophore is called a VESICLE, the

flask-shaped structures STERIGMA (pl. STERIGMATA); and because the spores are in chain formation, they are said to be CATENATE. (Fig. 138C.) In the type of chain produced from a growing tip, the youngest spore is always the newest one formed at the tip of the sterigma and the oldest spore is always on the distal end of the chain. Conidial chains developed in such a manner never branch and are said to be BASIPETALLY formed.

Although *Penicillium* forms spore chains from flask-shaped structures, sterigmata, in exactly the same way as *Aspergillus*, the *Penicillium* lacks the vesicle at the end of the conidiophore and in many species the conidiophores branch to give a brush-like appearance. (Fig 138B.) When seen under the microscope, these differences at once become apparent and cultures which grossly may appear similar can be identified accurately

A superficially similar but quite different type of spore chain formation is found in the genus *Hormodendrum* In this genus, the conidia are not cut off from a growing point but are developed from the conidiophore by a process of budding The first conidium produced on the conidiophore is a bud and it, in turn, produces a bud after reaching a certain size. Spore chains are formed by successive budding of the most distal conidium, the conidia remaining attached to each other *Hormodendrum* differs, therefore, from *Aspergillus* and *Penicillium* in that the proximal conidium is the oldest and the distal conidium is the youngest Conidial chains developed in this manner are said to be ACROPETALLY formed. During the development of acropetally formed chains, branching may occur since any of the conidia may have 2 buds, each developing its own chain

The few examples cited above give some of the methods of development and characteristic microscopic structures of the Fungi Imperfecti which are used by the mycologist to classify a fungus to its genus and species

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Chapter XXV

CONTAMINANTS

It is important to recognize the common contaminants which can be found on media inoculated with materials from human lesions *because etiologic significance has been ascribed erroneously to such* organisms. Non-pathogenic fungi may enter the cultures as air-borne contaminants, or can be introduced into the media directly with material taken from superficial or open skin lesions, sputum or other material. Frequently a single species of a contaminant appears *so regularly in a single patient's lesion that one is led to believe the* fungus to be the etiologic agent of his disease

The importance of the problem is such that we have kept a record of the contaminants which have occurred in our cultures for the past several years. The essential features of these non-pathogenic fungi are presented grossly by photographs and microscopically by drawings in order to illustrate the more important characteristics used for identification Most of these fungi have been identified as to genus only since many groups of the *Imperfecti have such closely related* species that identification is practical only in the hands of experts working with these groups Obviously, not all of the possible contaminants are presented as this would necessitate a monograph in itself It is hoped that the following plates will enable investigators *to identify quickly and easily most* of the contaminants usually encountered.

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Fig 139.—*A. Penicillium sp* The rapidly growing colony (50 mm. in diameter, eight days) is at first white, then becomes bluish-green and very powdery due to abundant spore production from the aerial mycelium

B Penicillium sp. Spore-bearing hyphae characteristically form a "Penicillus" or brush The conidia occur in unbranched chains (e) cut off from the tip of [illegible]

[illegible] color, texture, etc), the genus may be identified by the characteristic structure of the conidiophore which arises from vegetative hyphae either in, on or above *the agar at the end of which branching takes place to form the typical "Penicillus"* or brush

C. Paecilomyces sp. The rapidly growing colony (70 mm in diameter, five days) thinly covers the agar surface and becomes yellowish-brown and powdery due to an abundant production of conidia

[illegible] bearing hyphae [illegible] resemble the [illegible] which bends away [illegible]

E Scopulariopsis sp The slow growing colony (60 mm in diameter, eighteen days) is at first membranous, wrinkled and glabrous until aerial hyphae and conidia develop to give the culture a powdery, light brown appearance

[illegible] bearing hyphae cluster to resemble super- [illegible] is of [illegible] hore [illegible] ally [illegible] and [illegible] and [illegible] agent must be investigated most carefully before being reported as [illegible] agent of disease

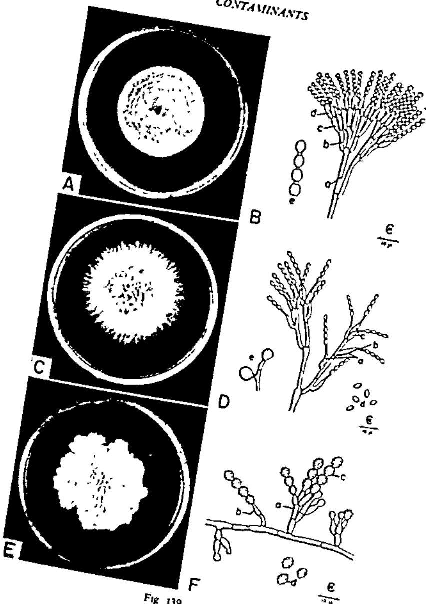
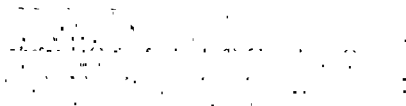


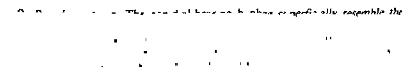
Fig 139

Fig. 139.—*A. Penicillium sp* The rapidly growing colony (50 mm. in diameter, eight days) is at first white, then becomes bluish-green and very powdery due to abundant spore production from the aerial mycelium



or brush

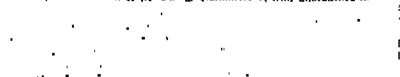
C Paecilomyces sp The rapidly growing colony (70 mm in diameter, five days) thinly covers the agar surface and becomes yellowish-brown and powdery due to an abundant production of conidia



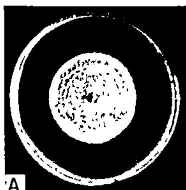
its characteristic taper into a long, conidial-bearing tube (b) which bends away from the main axis of the sterigma and the accessory cells or "macrospores" (e) found in or close to the surface of the agar distinguish this fungus from those of the genus *Penicillium*

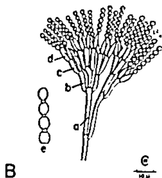
E Scopulariopsis sp The slow growing colony (60 mm in diameter, eighteen days) is at first membranous, wrinkled and glabrous until aerial hyphae and conidia develop to give the culture a powdery, light brown appearance

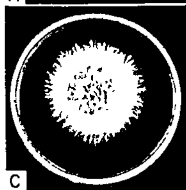
F Scopulariopsis sp. The conidia-bearing hyphae cluster to resemble super-

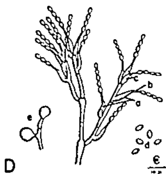


of disease


A


d
c
b
a
e
B


C


c
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a
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D



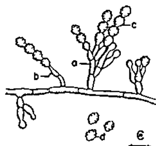

c
a
b
d

Fig. 140.—*A. Gliocladium sp.* The rapidly growing culture fills the petri dish in one week. It is at first white, then develops a dark green central zone, which spreads quickly over the surface of the colony. It usually is a more rapidly growing fungus than *Aspergillus* and *Penicillium* which it resembles.

B. Gliocladium sp. The conidial-bearing hyphae typically form a "Penicillus" as in *Penicillium*. From the conidiophore (a) branches (b) are developed from [illegible]

Gliocladium from *Penicillium*

C Aspergillus sp. The compact, slow growing colony (28 mm. in diameter, eight days) is at first white, then becomes bluish-green with sulfur-yellow areas scattered over the surface.

D Aspergillus sp. The conidial-bearing structure is an unbranched, non- [illegible] are cut off from the tips of the sterigmata, forming unbranched chains (e) and giving a rough appearance to the apically swollen conidiophore. Some species of *Aspergillus* develop perithecia (f) containing asci and ascospores (g) When these structures are encountered, the fungus is placed among the Ascomycetes in the genus *Eurotium*

[illegible] the petri dish in a few [illegible]

[illegible] The conidiophore (a) arises from the mycelium and imme- [illegible] tinuous budding [illegible] masses of ovate [illegible] ight air currents [illegible] septa (c and d).

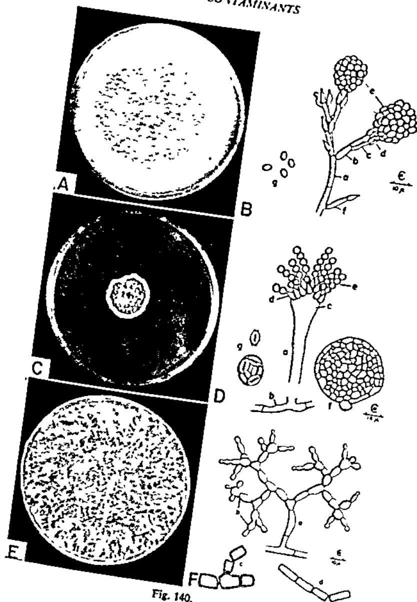


Fig. 140.

Fig 141.—*A. Verticillium sp.* The rapidly growing colony (75 mm in diameter, fifteen days) is at first white in the center with a thin radial growth which becomes powdery and pinkish-brown in color with the massive production of spores In test tube cultures, the macroscopic appearance of the growth may appear similar to the velvety or powdery growths of species of *Penicillium*

B Verticillium sp The conidiophores are elongate, verticillately arranged (in whorls) from the mycelium or from the ends of verticillately arranged branches of the mycelium (a). Single-celled conidia are borne in clusters from the ends of these conidiophores (b and c). The elliptical conidia (d) are dissociated easily *from the ends of the conidiophores and scatter throughout the preparation* unless the material is carefully manipulated when microscopic preparations are made.

C. Trichoderma sp The rapidly growing colony fills the petri dish in five days

distinguish these forms

tions are made with great care

E Cephalosporium sp The moderately fast growing colony (44 mm in diameter, seven days) is at first compact, deep rose in color, but becomes overgrown with a loose, white aerial mycelium

bear a spherical

tures)

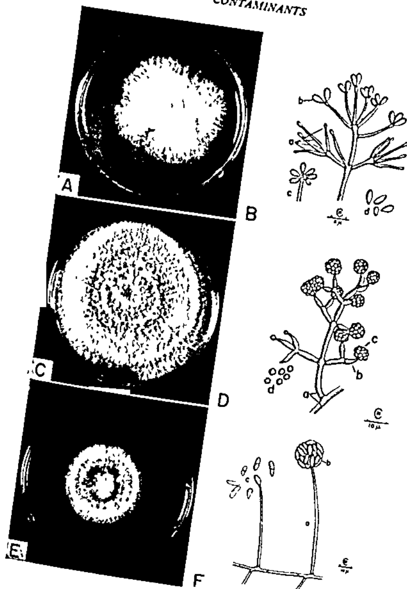


Fig 141

Fig. 142.—*A. Diplosporium sp.* The rapidly growing colony is at first white, cottony, thin, and later buff-colored and wooly. The reverse of the colony shows a deep red center surrounded by a brown, pigmented band which shades to orange at the periphery

B Diplosporium sp. Unbranched conidiophores (a) bear a globose cluster of elongate, two-celled conidia (d), showing a truncate point of attachment, which are held in the cluster by a sticky substance. There occur also multicelled, thick-

[illegible]

where it was probably a contaminant. Either this fungus or one closely related to it was the etiologic agent in a case of maduromycosis, *Cephalosporium sp.* Carrión, 1940

C. Trichothecium sp. The rapidly growing fungus (70 mm. in diameter, nine days) produces a white, wooly aerial mycelium which gradually becomes delicate pink in color.

[illegible]

F. Graphium sp Long, slender branches (a) produce small, pyriform conidia in clusters from swollen tips which show protuberances at points of attachment

[illegible]

1910 These forms are contaminants and should not be [illegible] trichum

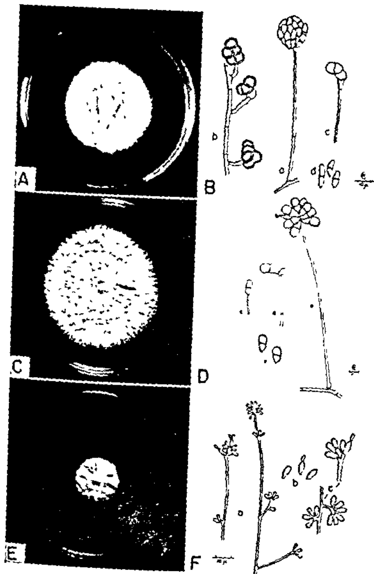


Fig 142

Fig 143.—*A. Fusarium sp.* The rapidly growing fungus (45 mm in diam five days) is at first white and cottony, but quickly develops a deep rose c in the center which shades to a light pink at the periphery. Because of the d rose pigmentation, this fungus often has been confused with *Trichophy (rosaceum) Megnini* (p 256)

B. Fusarium sp. Short hyphal branches give rise to verticillate conidiopho (a) which abstrict long, fusoid or sickle-shaped, pointed end, multisept conidia (c). These macroconidia are typical of the genus and need not be confus with the fuseaux which are produced sparingly in cultures of *Trichophyton.*

C. Oospora sp. The colony develops rapidly (90 mm in diameter, six day producing a light buff-colored, wooly aerial mycelium

D Oospora sp Long, slender hyphae (a) break up to form thin-walle rectangular cells (b) which take the place of spores as reproductive bodies (There seems to be no satisfactory classification of fungi which reproduce b mycelial fragmentation The genera *Oidium* and *Oospora* have been used ge erally to distinguish between obligate parasites of the ERYSIPHACEAE (ASCOM CETES) and other strictly saprophytic fungi, both of which reproduce by fragmen tation of their hyphae. In the medical literature, the yeastlike fungi reproducin by fragmentation usually are placed in the genus *Geotrichum*

E Mycelia sterila The colony develops rapidly (57 mm in diameter, seve days) as a white, cottony to wooly aerial growth

F. Mycelia sterila No spore forms are found in the cultures The term *M. sterila* should be regarded as designating a group of fungi rather than being applied to a single genus Many fungi found as contaminants do not produce characteristic spores that would allow them to be placed among the genera of the Imperfecti, i e, they are sterile Occasionally, however, fungi which produce spores under normal conditions of growth fail to do so when cultivated under unfavorable environmental conditions (media, temperature, etc) Attempts should be made, therefore, to cultivate non-spore-producing strains on a variety of media before placing them in the group *M sterila*

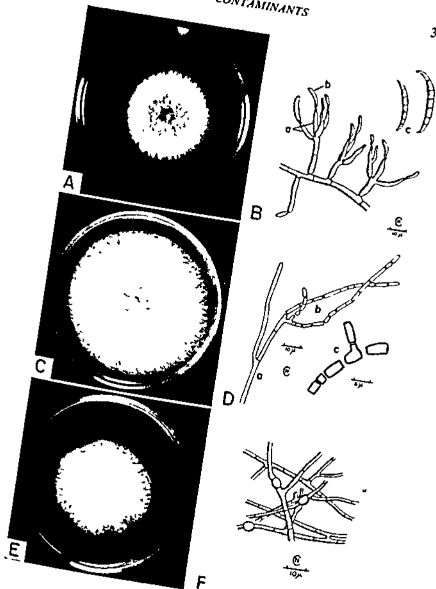


Fig. 143

Fig. 144.—*A. Streptomyces (Actinomyces) sp.* The slow growing, leathery colony (17 mm. in diameter, twenty-six days) becomes somewhat wrinkled, covered with a fine, chalky white surface, and has a distinct pungent musty odor. Many species produce a variety of colors due to characteristic pigment formation

B. Streptomyces (Actinomyces) sp. Long, slender branching hyphae (1 μ in diameter) produce spores by fragmentation or segmentation of the terminal branches. Microscopic preparations are not made easily, and it is usually necessary to study the morphology of the fungi from slide cultures These saprophytic organisms occur commonly in the soil and are frequent contaminants in the laboratory.

C. Cryptococcus sp The slow growing colony (21 mm in diameter, fourteen days) is white to cream-colored, moist, glistening, and, having the consistency of a bacterial colony, is easily picked up on a loop Other species produce various pigments and the colonies develop pink, red, or other colors

D. Cryptococcus sp. Mycelial development is lacking, the growth being composed entirely of round to oval, thin-walled, budding cells (a and b) Occasionally the buds, or daughter cells, produce buds before they have segmented entirely from the parent cell (c) and this results in the appearance of short chains of cells or small clusters of cells throughout the preparation Reproduction is carried on entirely by the budding of the thin-walled cells (blastospores). No endospores (ascospores) are found in these cultures, distinguishing this genus from the true yeasts where budding also occurs but in which ascospores are produced

E Ustilago zeae. The colony is slow growing (30 mm in diameter, twenty-two days) at first white, moist and easily picked up with a loop. It becomes folded, somewhat membranous and tan in color.

F. Ustilago zeae Microscopic preparations reveal elongate, spindle-shaped cells (sporidia) which rarely are seen attached to form a false mycelium These cells reproduce by budding and, with the consistency of the colony, the culture may be mistaken for a yeast.

This fungus is the corn smut parasite which causes marked hypertrophy of the seed in the ears of infected corn The masses of black spores, developed on these ears of corn are dispersed by the wind and frequently cause contamination of cultures

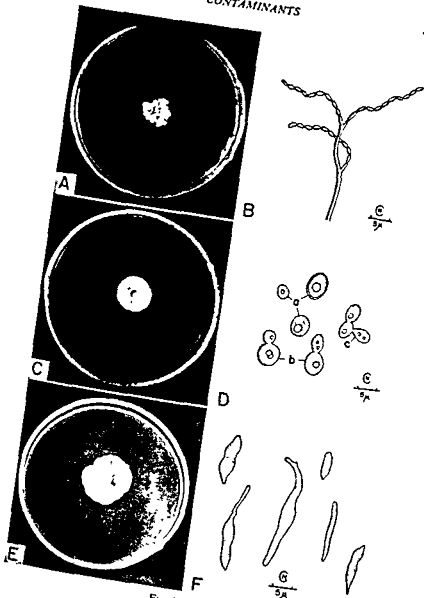


Fig. 144

Fig. 145.—*A. Hormodendrum sp.* The rapidly growing colony (65 mm. i[n] diameter, eight days) appears as a powdery, light green to grayish growth with [the] reverse of the colony of gray to black. Macroscopically, it may resembl[e] *Penicillium.*

B. Hormodendrum sp The conidial structures form characteristic "tree-like" clusters. Conidiophores of various lengths (a) support *branching* chains o[f] conidia (b) which are elongate, ovate, separated by dark disjunctors and forme[d] by continuous budding They are single-celled in young cultures, but later ma[y] become divided by septation to form many *two-celled conidia.* The mycelium, conidiophores and conidia are dark brown in color.

C. Alternaria sp. The rapidly growing colony (40 mm in diameter, four days) develops its mycelium close to the agar surface, grayish at first, then becoming [illegible]

E. Helminthosporium sp. The rapidly growing colony (40 mm in diameter, five days) is at first grayish in color, then forms a matted, black, depressed central mycelium with raised grayish periphery

F. Helminthosporium sp The conidia occur in clusters on short, knotted *conidiophores (a). They are long, rounded-ovate* with several transverse septa (b). The conidiophore develops as a branch from the mycelium, becomes swollen on the end and produces a single conidium to one side and slightly below the tip [illegible]

in color.

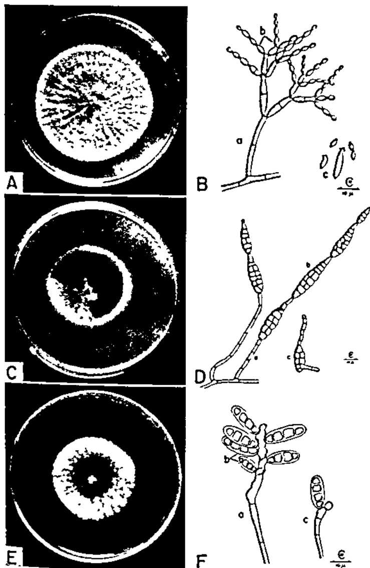


Fig. 145.

Fig 146.—*A. Nigrospora sp.* The rapidly growing fungus (70 mm in diameter five days) forms a compact, wooly, white aerial growth which becomes gray due to the black sporulating mycelium on the surface of the agar. The reverse of the culture is black.

B. Nigrospora sp. The conidia are black, shiny, depressed-globose (b) and are produced from swollen or characteristically ampulliform conidiophores (a) When these black, shiny conidia are produced in great numbers, the colony becomes grayish to dark gray in color and the reverse of the colony becomes quite black.

C. Montospora sp. The moderately fast growing fungus (35 mm. in diameter, twelve days) forms a colony of compact, light gray aerial mycelium with dark gray center showing some evidence of radial folding

D. Montospora sp. The conidia are produced in great quantity in the submerged [illegible] spores bear a superficial resemblance to those found in *Monosporium*, but are small, sessile or on very short conidiophores and appear in the submerged hyphae, not from the aerial mycelium.

E. Pullularia (Dematium) pullulans. The fungus develops a heaped, wrinkled, black, shiny, leathery-appearing colony with grayish fringe of submerged mycelial growth. The surface becomes shiny in appearance due to the mass of conidia produced.

F. Pullularia (Dematium) pullulans Thick-walled, black, large cells from the hyphal strands make up the bulk of the mycelium (b) *Some of these germinate,* forming short tubes which immediately bud off several small, pyriform conidia (c) Throughout a microscopic preparation may be seen long, delicate, thin-walled hyphae, the cells of which produce numerous conidia directly from their walls (a). These conidia may bud, producing a mass *of shiny material* over the surface of the culture

Macroscopically, the culture may resemble dark-colored strains of *Sporotrichum.* The thick-walled, black, large cells (b) and the budding spores (a) *should differentiate this fungus from* any other

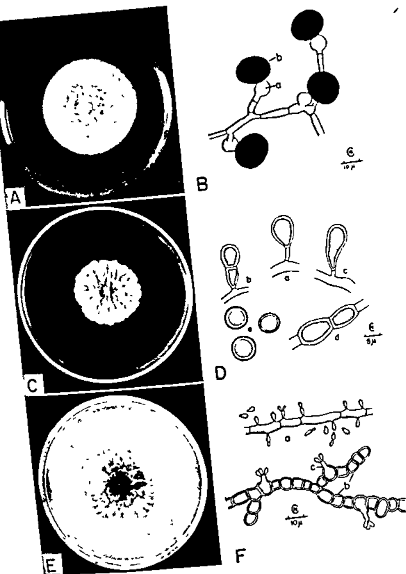


Fig. 146

Fig. 147.—*A. Hemispora sp.* The slow growing colony (11 mm in diameter, eight days) is heaped, brittle and deep brown in color.

B. Hemispora sp Chains of conidia are formed on the ends of short hyphal branches from a tubular structure limited by a constriction in the hypha (a), close septations divide the contents of the tube into square, thick-walled, deep staining segments These are pushed forward by the formation of new segments cut off by the conidiophore at the point of constriction. The tubular wall ruptures; the conidia are held together for a brief period, then separate to form round, thick-walled, roughened spores The conidiophore pushes ahead at the base of the first formed chain of conidia (b), forms another chain and by continued growth several lateral chains are formed (c).

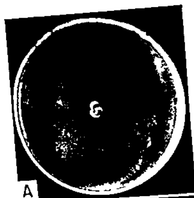
This fungus has been reported from osteoperiostitis, cold abscesses and sporotrichoid lesions

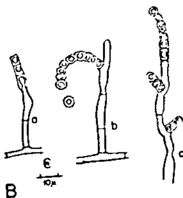
C. Phoma sp. A moderately fast growing colony (35 mm in diameter, eight days) with a granular appearance due to small, raised pink and black areas overgrown with a grayish, loose aerial mycelium. The reverse of the colony is black.

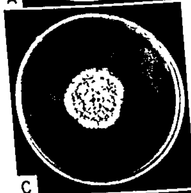
D. Phoma sp Dark bodies, pycnidia, scattered through the culture and visible in mass to the naked eye, appear as flask-shaped vesicles microscopically (a). The pycnidia, when crushed, are seen to be filled with small, single-celled hyaline spores (b) These structures are asexual fruiting bodies inside of which conidiophores are clustered and from which masses of conidia are produced

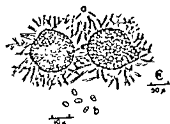
E Pleospora sp A moderately fast growing colony (45 mm in diameter, seven days) showing a compact, radially grooved surface tan to greenish in color. The reverse of the colony is brown to black

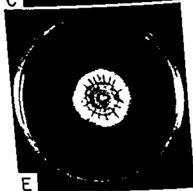
F Pleospora sp The flask-shaped perithecium (a) contains asci (b) with eight muriform ascospores (c) These fruit-bodies, perithecia, must be crushed to free the asci for examination.











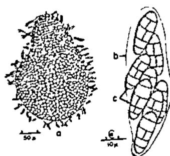


Fig. 147

Fig. 148 —*A. Mucor sp.* The rapidly growing fungus fills the petri dish in five days with an abundant growth of floccose aerial mycelium which is at first white, then dark gray.

B. Mucor sp. The non-septate vegetative mycelium gives rise to numerous unequalled length sporangiophores (a) which branch irregularly and bear terminal globose, spore-filled sporangia (b). The wall of the sporangium is easily broken, scattering the elliptical spores (e), leaving a fragment of the sporangial wall (*collarette*) at the base of the spherical columella (c). This structure is the swollen end of the sporangiophore which extends into the sporangium and is seen only when the sporangial wall ruptures and the mass of spores are dispersed

C Rhisopus sp The rapidly growing fungus fills the petri dish in five days with a dense, cottony aerial mycelium which is at first white, then dark gray.

D. Rhizopus sp. Among the non-septate aerial mycelia are numerous stolons (runners) (e) which connect fascicles or groups of unbranched sporangiophores (b) arising at the point of contact of the stolon with some surface (medium or glass), at which point a tuft of root-like hyphae or rhizoids (a) are produced The sporangiophores are terminated by black, globose, spore-filled sporangia (d). The swollen tip of the sporangiophore, columella, extends into the sporangium (c) and is clearly visible (f) when the sporangial wall ruptures Thus genus is differentiated from *Mucor* by the presence of stolons, rhizoids and the unbranched sporangiophores arising in fascicles at a point opposite the rhizoids.

E. Syncephalastrum sp The rapidly growing fungus fills the petri dish in four days with a dense, cottony aerial mycelium which is at first white, then dark gray to almost black

F. Syncephalastrum sp. The sporangiophores are short branches of the aerial hyphae (a) with greatly swollen tip (b), bearing long, finger-like tubular sporangia (c) in which are formed long chains of spores (e and f) These tubular sporangia which radiate from the tip of the sporangiophore are peculair to this genus and give the spore-bearing structures the general appearance of *Aspergillus* spore heads under low magnifications Occasionally one or two spored sporangia are found (d), but the majority are elongate (f) and contain a number of spores

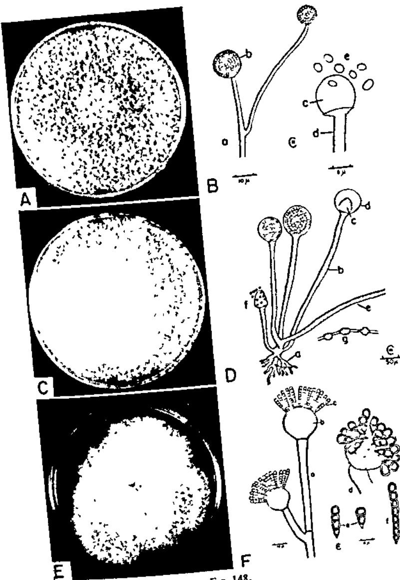


Fig. 148.

APPENDIX

MYCOLOGIC METHODS

Direct Microscopic Examination

1. **Pus** should be examined unstained by placing a drop of the pus on a slide and gently pressing it under a cover glass to make a thin smear. It is important that the condenser be racked down to reduce the light reaching the objective. If necessary, the preparation may be cleared by placing the pus in a drop of 10 to 20 per cent potassium hydroxide, adding a coverslip and gently warming the slide. The material should be examined for sulfur granules (Fig. 7), budding cells (Figs. 20, 71), budding cells with a capsule (Fig. 60*A*), or large cells with endospores (Fig. 32)

NOTE —At times, it may be difficult to distinguish round or oval artefacts from fungus cells. If the fresh preparation be rimmed with vaseline and allowed to stand at room temperature for several days, the yeast cells of the filamentous fungi often germinate and produce hyphae in the pus.

2. **Spinal fluid** should be examined in the same way as pus, except that the spinal fluid should be centrifuged and the sediment examined directly. If oval or budding cells are seen and *Cryptococcus* infection is suspected, a bit of the sediment should be placed in a drop of India ink to demonstrate the presence of capsules (Fig. 60*B*).

3 **Sputum** is examined in the same way as pus A smear, fixed with heat, should be stained by Gram's method to demonstrate filaments of *Actinomyces* (Fig. 8), or the yeast cells and filaments of *Candida* (Fig. 71*B*.) Acid-fast stains also should be done to demonstrate *Nocardia*.

4. **Open ulcers** should be examined in the same way as pus or sputum The materials should be taken from the active margins of the lesion, and potassium hydroxide preparations should be made if clearing is necessary

5. **Superficial skin lesion** scrapings should be placed between flamed glass slides, wrapped in paper for transportation to the laboratory and the scrapings examined unstained in 10 to 20 per cent potassium hydroxide (Fig. 116)

6. **Hair** should be examined in the same way as scrapings from the superficial skin (Fig. 115).

7. **Nail** scrapings are examined in the same way as skin and hair, but more time often is required for clearing of the preparation by potassium hydroxide.

Cultural Methods

All materials from suspected cases of mycotic infections should be cultured for fungi regardless of whether or not fungus cells are found on direct examination. As a routine procedure, it is suggested that blood agar plates be streaked and Sabouraud's glucose agar slants inoculated with suspected materials The blood agar plates or slants should be incubated at 37° C. and the Sabouraud's agar slants at room temperature.

If *Actinomyces bovis* is suspected, material also should be inoculated into veal infusion agar shake tubes.

For identification of *Candida albicans*, corn meal agar should be inoculated in order to demonstrate chlamydospore formation. The directions for inoculation can be found in the chapter on moniliasis (page 142)

Microscopic examination of the yeastlike growth is made by suspending a loopful of the culture in a drop of water and covering the preparation with a coverslip.

The filamentous fungi must be placed in a mounting fluid such as lactophenol cotton blue and the fungus elements gently separated with teasing needles

Media

Sabouraud's Glucose Agar

Dextrose (or maltose)	40 Gm
Agar	35 Gm
Peptone (Fairchild's)	10 Gm
Distilled water	1,000 cc.

Melt in autoclave, filter through cotton gauze and tube Autoclave at 15 lbs for 15 minutes and slant

Blood Agar and Veal Infusion Agar

Prepared by the routine methods used in most bacteriologic laboratories

Corn Meal Agar

Corn meal	40 Gm
H_2O	1,000 cc.
Agar	20 Gm

Simmer corn meal and water for one hour Filter through gauze Measure and bring volume back to 1,000 cc Add agar and melt in autoclave Filter through two layers of cotton and gauze Tube and sterilize in autoclave at 15 lbs pressure for 15 minutes

NOTE.—*Candida albicans* will not produce chlamydospores regularly on bacto-corn meal agar

Stain

Lactophenol Cotton Blue

Phenol crystals	20 Gm.
Lactic acid	20 cc
Glycerol	40 cc.
Distilled water	20 cc.

Dissolve by heating gently under a hot water tap. Add 0.05 Gm cotton blue

PATHOLOGIC METHODS

Staining by Gram's method is of value in the identification of certain fungi in tissue sections. MacCallum's modification of Goodpasture's method has been used with success in this laboratory.

Fixation in Zenker's or Helly's solution is preferable, and thin sections should be cut from paraffin-embedded blocks.

Staining Solutions

Goodpasture's Stain

Basic fuchsin	0.59 Gm
Aniline	*1 cc*
Phenol crystals	1 Gm.
Alcohol, 30 per cent	100 cc

Stirling's Crystal Violet Stain

Gentian violet (crystal violet)	5 Gm
Alcohol, absolute	10 cc.
Aniline	2 cc.
H_2O	88 cc.

This solution keeps remarkably well

Gram's Iodine Solution

Iodine	1 Gm.
Potassium iodide	2 Gm
Distilled water	300 cc.

Method of Staining

1. Stain sections for 10 to 30 minutes in Goodpasture's stain
2. Wash in water.
3. Differentiate in strong formalin for a few seconds, until the bright red color changes to a clear rose
4. Wash in water.
5. Counterstain in a saturated aqueous picric acid solution (about 1 22 per cent) 3 to 5 minutes or less, until section assumes a purplish-yellow color.
6. Wash in water.
7. Differentiate in 95 per cent alcohol. This causes the red color to reappear; some of it is washed out together with some of the yellow color
8. Wash in water.
9. Stain for 5 minutes in Stirling's crystal violet solution

10 Wash in water.

[illegible]

14. Rinse with two changes of xylol and mount in balsam.

RESULTS.—Gram-positive organisms blue, gram-negative organisms red; all other tissue elements various shades of red to purple.

IMMUNOLOGIC METHODS

The Complement Fixation

This test for antibodies to fungi may be performed in any laboratory in which the Wassermann test is a routine procedure. Except for the substitution of a fungus suspension for the beef heart antigen, all reagents such as complement, amboceptor and red cell suspensions should be employed in the same quantities as is used in the Wassermann technique. For example, in this laboratory, the Wassermann test is performed by using 0.2 cc. quantities each of patient's serum, complement and antigen. After 3-hour fixation in the ice-box, 0 4 cc. of sensitized sheep's cells are added and incubated in the 37° C. water [illegible]

The antigens are made by preparing saline suspensions of the fungus cultures. The growth should be scraped off the surface of the medium and transferred to a sterile mortar and ground with a pestle while still dry or after adding only a small amount of physiologic saline. Thus, a paste is made, and saline should be added slowly while the grinding is continued in order to make a uniform suspension

Before using the suspension, both the anticomplementary and the hemolytic titers should be determined The anticomplementary titer is measured by adding 0 2 cc. quantities of various dilutions of the fungus suspension to 0 2 cc of complement and 0 2 cc of saline. After the mixture has been in the ice-box 3 hours, 0 4 cc. of sensitized cells are added. After 30 minutes' incubation at 37° C, the greatest dilution of antigen producing any inhibition of hemolysis is recorded The hemolytic titer is determined by following the same procedure but omitting the addition of complement.

As yet, fungus antigens for use in the complement fixation test have not been standardized In our tests, we have selected arbitrarily a suspension four times as dilute as the greatest dilution showing anticomplementary properties Since the anticomplementary titer of

the antigen is not a function of its combining power, such a method of antigen standardization leaves much to be desired. However, it has been satisfactory in that false positive tests have not been obtained, although the sensitivity of the test is not as great as could be expected if better methods of standardization existed.

The protocol of the usual procedure is as follows·

Back Row

Tube No	1	2	3	4	5	6	7	8
Patient's	0.2 cc	0 2 cc.	0 2 cc.	0.2 cc.	0.2 cc	0 2 cc.	0.2 cc.	0 2 cc
serum	Und	1–2	1–4	1–8	1–16	1–32	1–64	1–128
Complement	0 2 cc.	0 2 cc	0 2 cc.	0 2 cc.	0 2 cc	0 2 cc.	0 2 cc.	0 2 cc
Antigen	0 2 cc.	0 2 cc.	0 2 cc.	0 2 cc	0 2 cc.	0 2 cc.	0 2 cc	0 2 cc

Front Row

Patient's	*0 4 cc.*	*0.4 cc.*	*0 4 cc*	—	—	—	—	—
serum	Und	1–2	1–4	—	—	—	—	—
Complement	0 2 cc.	0.2 cc	0 2 cc.	—	—	—	0 2 cc.	—
Antigen	—	—	—	—	—	—	0 4 cc	0 4 cc
Saline	—	—	—	—	—	—	—	0 2 cc

Place in the ice-box for 3 hours Add 0 4 cc. sensitized cells to all tubes and incubate in the 37° C. water bath until the controls are hemolyzed completely. In a satisfactory test, the serum controls in the front row (tubes 1, 2 and 3) should be completely hemolyzed, as well as the antigen control (front row, no 7). The hemolytic control (front row, no 8) should show no hemolysis

Sometimes the fungus suspensions are so cloudy that reading of the tests may be difficult, the suspension should be centrifuged and the degree of hemolysis noted by examination of the supernates.

Preparation of the Vaccines

Vaccines can be made by preparing fungus suspensions in the same manner as that described above for preparation of suspensions for use in the complement fixation test The suspensions should be diluted in sufficient saline to give the vaccine the density of a light "ground glass" appearance. The vaccine is heated in a 60° C. water bath for at least 2 hours, tested for sterility and preserved by adding 0 3 per cent tricresol or merthiolate 1.20,000

Such vaccines are used undiluted for skin testing by injecting 0 1 cc intracutaneously. The same vaccines, appropriately diluted, also may be used for desensitization.

DERMATOLOGIC METHODS

Ultraviolet Radiation (Wood's Light)

A simple Wood's light may be constructed by following the outline given in Lewis and Hopper's book; or it may be purchased.*

The light has its greatest practical application in the diagnosis and management of tinea capitis since one not only can establish the diagnosis but also is able to follow the results of treatment and determine when all foci have been irradicated successfully. Tinea versicolor is another of the mycoses which can be followed from diagnosis to cure. It must be remembered, however, that many organic and inorganic substances fluoresce, including teeth, nails, keratin, petrolatum, salicylic acid and porphyrins

The Wood's light has not been used in the study of all species of fungi, and there is some disagreement as to specific fluorescence. The following table presents some of the data which have been obtained.

APPEARANCE UNDER FILTERED ULTRAVIOLET RADIATION

ORGANISM	CLINICAL	CULTURE
Microsporum Audouini	Bright clear green	Dull grayish
M canis	Bright clear green	Lavender blue central portion to gray border
M gypseum	Light greenish	Cinnamon brown
Trichophyton ferrugineum	None	Yellowish tan
T Schoenleini	Dull greenish	Olive gray
T violaceum	Dull whitish	Violet (not true fluorescence)
T tonsurans	Dull whitish	Dark olive
T. sulfureum	Dull grayish	Grayish
T mentagrophytes	None	Blue violet center to fawn border
T rubrum	None	Dull dark olive
Epidermophyton floccosum	None	Dark dull olive
Malassezia furfur	Yellowish brown	Unknown
Candida albicans	None	Yellowish brown

FORMULARY

I. Wet Dressings

1. Potassium Permanganate Solution (1 4000) Gm or cc

℞	Potassium permanganate	0 25
	Water	1000 0

Sig Use for soaks or wet dressings

* Westinghouse Electric & Manufacturing Co, Long Island City Strobelite Co, New York, N. Y

2. Physiologic Saline Solution

		Gm. or cc.
℞	Sodium chloride	9 0 (0.9%)
	Distilled water	1000 0

Sig: Use for soaks or wet dressings

3. Boric Acid Solution

		Gm or cc.
℞	Boric acid	30 0
	Water	1000 0

Sig: Use for soaks or wet dressings

4. Burow's Solution

		Gm. or cc.
℞	Liquor alumini acetatis N F. VII	500 0

Sig: Dilute 1:20 (approx. 0 25%) or 1:40 (approx. 0 125%) for soaks or wet dressings

5. Magnesium Sulfate Solution

		Gm or cc
℞	Magnesium sulfate	15.0 (1.5%)
	Distilled water	1000 0

Sig: Use for soaks or wet dressings

6. Diluted Solution Sodium Hypochlorite

		Gm. or cc.
℞	(Modified Dakin's solution 0 5%)	1000 0

Sig: Dilute with equal parts distilled water and use for soaks or wet dressings

II. Dusting Powders

1. Dusting Powder (Army general issue foot powder)

		Gm. or cc
℞	Salicylic acid	2 0 (2%)
	Boric acid	6 0 (6%)
	Zinc stearate	3.0 (3%)
	Exsiccated alum	1 0 (1%)
	Starch	10 0
	Talcum	78 0

Sig Apply locally as directed

2. Thymol-Iodide, Salicylic-Acid Dusting Powder

		Gm or cc
℞	Thymol iodide	0 6 (1%)
	Salicylic acid	1 8 (3%)
	Talcum powder	60 0

Sig. Use locally as directed

3. Dusting Powder (Calcium Propionate

		Gm or cc
℞	Calcium propionate	9 0 (15%)
	Talcum powder	60 0

Sig· Use locally as directed

III. Ointments

1. Modified Whitfield's Ointment N F. VII (full strength)

		Gm or cc
℞	Salicylic acid	3 6 (6%)
	Benzoic acid	7.2 (12%)
	Petrolatum	60 0

Sig: Apply as directed

2. Sulfur-Salicylic Ointment

	Gm. or cc.
℞ Sulfur ppt.	1 8 (3%)
Salicylic acid	1 8 (3%)
Aquaphor (or petrolatum) q s	60 0

Sig. Apply as directed

3. Ammoniated Mercury Ointment U.S P. XII

	Gm. or cc.
℞ Ammoniated mercury	3 0 (5%)
White ointment q s	60.0

Sig· Apply locally as directed

4. Dioxyanthranol Ointment

	Gm. or cc
℞ Anthralin (or cignolin)	0 15 (0.25%)
Petrolatum q.s.	60 0

Sig· Apply as directed

5. Strong Sulfur, Salicylic-Acid Ointment

	Gm. or cc.
℞ *Sulfur ppt.*	6 0 (10%)
Salicylic acid	6 0 (10%)
Lanolin	30 0
Rose water ointment	30 0

Sig Rub into affected areas as directed

6 Chrysarobin Ointment

	Gm or cc.
℞ Chrysarobin	3 0 (5%)
Aquaphor or	
Rose water ointment	60 0

Sig Apply locally as directed

7. *Ichthyol Ointment*

	Gm. or cc.
℞ Ichthyol	1.8 (3%)
Zinc oxide ointment	60 0

Sig Apply locally as directed

8. Iodine Ointment

	Gm. or cc
℞ *Iodine crystals*	3 0 (5%)
Aquaphor or	
Lanolin	60 0

Sig Apply locally as directed

9 Quinolor Ointment (Quinolor compound ointment, Squibb)

	Gm. or cc.
℞ Chlorhydroxyquinolin (quinolor)	0 3 (0 5%)
Benzoyl peroxide	6 0 (10%)
Aromatic oils	0 15(0 24%)
Vehicle (inert) q s	60 0

Sig Apply as directed

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